CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 20 JULY 2023

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01 (zilebesiran)
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021 Amendment 1, 20 April 2021 Amendment 2, 09 June 2021 Amendment 3, 09 December 2021 Amendment 4, 22 March 2022 Amendment 5, 04 November 2022 Amendment 6, 20 July 2023
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Sponsor Contact:	[redacted] MD [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document as Alnylam Executive Leadership Member
Signing Time: 24-Jul-2023 | 10:45 AM EDT
06848DA7D4CE4DF8B4902C2A88D6C2FD

[redacted] MD, PhD
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Alnylam Pharmaceuticals, Inc.

24-Jul-2023 | 10:45 AM EDT

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01 (zilebesiran)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 150 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM • Change from baseline at Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6 Other Secondary Endpoints • Time-adjusted change from baseline in 24-hour mean SBP and DBP, assessed by ABPM

Objectives	Endpoints
	• Change from baseline in 24-hour mean DBP, assessed by ABPM • Change from baseline in office SBP and DBP • Change in serum AGT • Change in daytime and nighttime blood pressure (including dipping pattern)
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM control and response rates • Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in pulse pressure assessed by ABPM and office blood pressure
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To assess the long-term treatment effect of ALN-AGT01 (through Month 36)	• Change from baseline in SBP and DBP assessed by office blood pressure and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers). Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may have been eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reached Month 12 prior to availability of the OLE study, they may have continued their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study was open and then transition. Upon implementation of Amendment 6, the DB Extension period will be closed because a separate OLE study will not be conducted. Patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 12. Patients in the DB Extension period will complete end of treatment (EOT) assessments at Month 18, 24, 30, or 36 (whichever visit comes first) and enter the Safety Follow-up period.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive, at time of initial informed consent) with untreated hypertension or on stable therapy with up to 2 antihypertensive medications. Patients should have a daytime mean systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Before Amendment 6, patients who entered the DB Extension period continued their current blinded dosing regimen from the 12-month DB period. Upon implementation of Amendment 6, the DB Extension period will be closed because a separate OLE study will not be conducted. Patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 12. For patients in the DB Extension period, patients will receive their last dose of study drug if their next visit is at Month 15, 21, 27, or 33 (whichever comes first). Patients will not receive study drug at other visits in the DB Extension period.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 36 months. The estimated total time on study for each patient is up to 47 months, including up to 2 months of screening, followed by up to 36 months of treatment, and up to 12 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response signal in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.

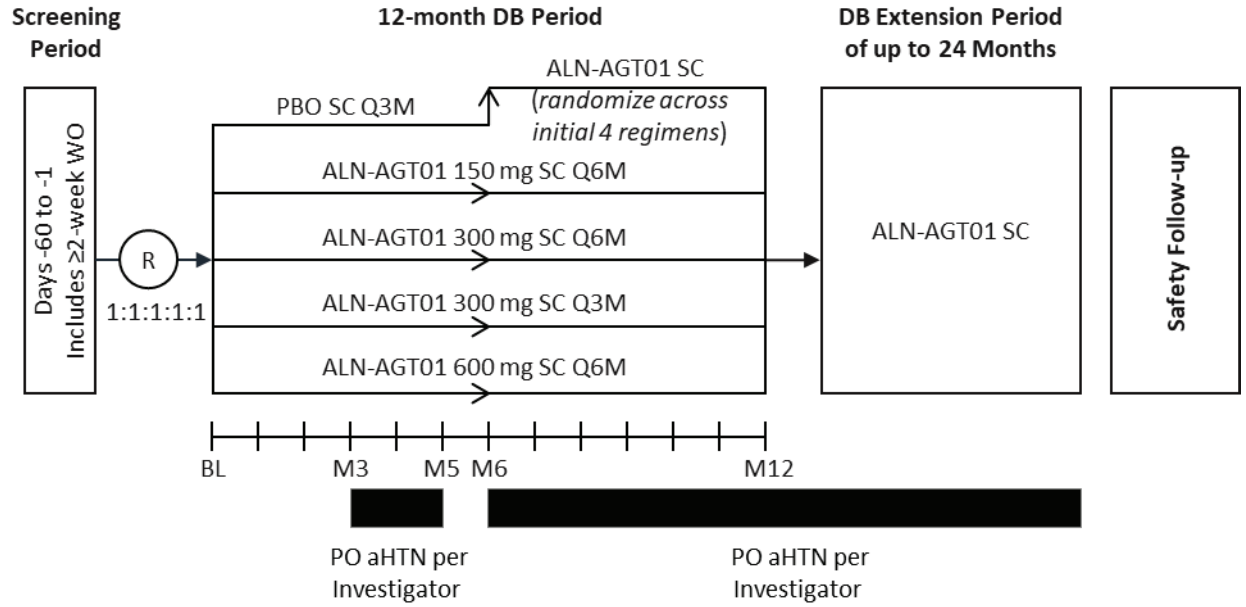
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

For the primary analysis for the 6-month placebo-controlled DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All ALN-AGT01 Treated Set will be used to summarize the efficacy and safety of ALN-AGT01 throughout the entire DB period (including DB Extension period).

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; EOT=end of treatment; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.

Note: Patients may have been eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reached Month 12 prior to availability of the OLE study, they may have continued their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study was open and then transition. Upon implementation of Amendment 6, the DB Extension period will be closed because a separate OLE study will not be conducted. Patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 12. Patients in the DB Extension period will complete all scheduled assessments and receive their planned dose of study drug if their next visit is at Month 15, 21, 27, or 33 and return to complete EOT assessments at their next scheduled visit (Month 18, 24, 30, or 36) and then enter the Safety Follow-up period. If the next visit is Month 18, 24, 30, or 36, patients should complete EOT assessments and enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 18, 24, 30, or 36.

Note: Patients who were previously taking antihypertensives at screening should undergo a washout of these medications for at least 2 weeks during the Screening period (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																
Study Visit		**Screening Period**	**Double-blind Period[a]**													**DB Extension Period[a]**	**M36/EOT/ET**	**Safety Follow-up**
				W2	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M6.5**	**M7**	**M8**	**M9**	**M12**			**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-60 to -1**	**D1**	**D15±2**	**D29 ±2**	**D57 ±7**	**D85 ±7**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D183 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D337±7**	**Q3M ±14**	**D1009±14**	**±14**
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 2 to 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Section 6.2	X			X		X			X		X		X	X		X[g]	
HBPM[c,f]	Section 6.2	X	At least once per week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	

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Neurological evaluation and symptom-directed physical exam	Section 6.5.3						X			X				X		X		X
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X					X	X[h]	X	

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Study Visit		**Screening Period**	**Double-blind Period[a]**												**DB Extension Period[a]**	**M36/EOT/ET**	**Safety Follow-up**
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Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)[i]	Section 6.5.5.2		X				X			X				X	X	X	X	X
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: AngI/II, renin and aldosterone	Section 6.3		X	X	X	X	X			X					X		X[g]	
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									
Study drug administration	Section 5.2.2		X				X			X				X	X	X		

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AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous																
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DB=double-blind; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAAS biomarkers (renin and aldosterone, and AngI/II) should be performed before physical examinations and 12-lead ECGs.
- Patients may have been eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reached Month 12 prior to availability of the OLE study, they may have received a dose of ALN-AGT01 at the Month 12 visit and continued their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study was open and then transition. Upon implementation of Amendment 6, the DB Extension period will be closed because a separate OLE study will not be conducted. Patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 12. Patients in the DB Extension period will complete all scheduled assessments and receive their planned dose of study drug if their next visit is at Month 15, 21, 27, or 33 and return to complete EOT assessments at their next scheduled visit (Month 18, 24, 30, or 36) and enter the Safety Follow-up period. If the next visit is Month 18, 24, 30, or 36, patients should complete EOT assessments and enter the Safety Follow-up period. Patients will not receive a dose of study drug at Months 18, 24, 30, or 36.

- Patients will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator.
- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**
[b] When applicable, pregnancy test results must be known prior to dosing.
[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 2 weeks of washout (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).
[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.
[e] ABPM recordings associated with dosing visits must be obtained within 2 weeks prior to randomization and within 7 days before dosing visits after Day 1 and results reviewed before dosing.
[f] HBPM should be measured at least once per week in the morning upon waking. HBPM may be measured more frequently in some patients, per Investigator discretion, if more frequent measurement is warranted (eg, during screening if patients are undergoing washout and between Months 5 and 6 if oral antihypertensives are temporarily held). HBPM is not required at times when ABPM is being assessed.
[g] ABPM and collection of RAAS biomarkers should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12, and ABPM should only be performed at ET if the patient has not had an ABPM within the last 3 months. These assessments should not be performed at Month 36.
[h] Fasting plasma laboratory samples should only be collected at Month 18.
[i] The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour:minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
LFT	Liver function test
MAO	Monoamine oxidase
MMRM	Mixed model for repeated measurements
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal
ZS-9	Sodium zirconium cyclosilicate

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01 (zilebesiran), a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may have been eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reached Month 12 prior to availability of the OLE study, they may have continued their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study was open and then transition. Upon implementation of Amendment 6, the DB Extension period will be closed because a separate OLE study will not be conducted. Patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period and then enter the Safety Follow-up period. Patients in the DB Extension period will complete end of treatment (EOT) assessments at Month 18, 24, 30, or 36 (whichever visit comes first) and enter the Safety Follow-up period.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is

associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension and to overcome the limitations of current therapies is a key unmet need.[Dzau 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of

conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM • Change from baseline at Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6 Other Secondary Endpoints

Objectives	Endpoints
	• Time-adjusted change from baseline in 24-hour mean SBP and DBP, assessed by ABPM
	• Change from baseline in 24-hour mean DBP, assessed by ABPM • Change from baseline in office SBP and DBP • Change in serum AGT • Change in daytime and nighttime blood pressure (including dipping pattern)
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM control and response rates • Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in pulse pressure assessed by ABPM and office blood pressure
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile

Objectives	Endpoints
• To assess the long-term treatment effect of ALN-AGT01 (through Month 36)	• Change from baseline in SBP and DBP assessed by office blood pressure and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers [CCBs]).

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, home blood pressure

monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM).[Williams 2018] Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may have been eligible to participate in a separate ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reached Month 12 prior to availability of the OLE study, they may have continued their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study was open and then transition.

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Upon implementation of Amendment 6, the DB Extension period will be closed because a separate OLE study will not be conducted. Patients in the 12-month DB period will continue dosing and assessments as scheduled through Month 12. Upon completion of predose assessments at the Month 12 visit, patients will enter the Safety Follow-up period. Patients will not receive a dose of study drug at the Month 12 visit. For patients in the DB Extension period:

- If the next visit upon implementation of Amendment 6 is Month 15, 21, 27, or 33, the patient should complete the scheduled assessments and receive the planned dose of study drug. Patients should return for their next scheduled visit (Month 18, 24, 30, or 36) to complete EOT assessments and enter the Safety Follow-up period. Patients will not receive a dose of study drug at the Month 18, 24, 30, or 36 visit.
- If the next visit upon implementation of Amendment 6 is Month 18, 24, 30, or 36, the patient should complete EOT assessments and enter the Safety Follow-up period. Patients will not receive a dose of study drug at the Month 18, 24, 30, or 36 visit.

Patients will be considered as completing study drug if they received all planned doses during the 12-month DB period (Day 1 and Months 3, 6, and 9) and completed the Month 12 visit.

Safety Follow-up Period

Patients will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or until 12 months after their last dose of study drug, whichever comes earlier. During the Safety Follow-up period, patients should return to their pre-study medical care (usual care).

Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 36 months. The estimated total time on study for each patient is up to 47 months, including up to 2 months of screening, followed by up to 36 months of treatment, and up to 12 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for 2 to 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe hypertension (office SBP ≥180 mmHg or DBP ≥120 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a CCB and/or thiazide/thiazide-like diuretic may be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 2 to 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each

patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer (or with sodium zirconium cyclosilicate [ZS-9]), if available, for treatment of potential hyperkalemia.[Georgianos 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for

close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Before Amendment 6, patients who entered the DB Extension period continued their current blinded dosing regimen from the DB period. Upon implementation of Amendment 6, patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period but will not be eligible to enter the DB Extension period and receive a dose of study drug at Month 12.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria

and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. During the course of the study, serum AGT, plasma PK, and treatment assignment using dummy IDs will be made available to a small, independent pharmacometrics team at the Sponsor that will not be involved in the conduct or oversight of the study. After the last patient completes the Month 3 visit and prior to the last patient's Month 6 visit, a limited amount (ie, one-third) of SBP data will be made available to this small, independent pharmacometrics team for preliminary PK/PD modeling. After the database lock to support the analysis of Month 6 data is complete, all other Sponsor personnel will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after final database lock. The Sponsor and all site personnel will be blinded to serum AGT results until their respective unblinding. Serum AGT results will not be reported to site personnel until after the last patient completes the assessments at the Month 12 visit.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the Safety Follow-up visits as described in Section 3.1.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive, at time of initial informed consent
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with up to 2 antihypertensive medications. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Daytime mean SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to this ABPM (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics [eg, chlorthalidone] or CCBs [eg, amlodipine]).

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension (including, but not limited to, renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, aortic coarctation, or due

to known history of moderate-to-severe obstructive sleep apnea not treated with continuous positive airway pressure therapy)

2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 2 to 4 weeks of washout:
   a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
   b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
   c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
   d. Elevated potassium >5 mEq/L
   e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational. Patients who are in follow-up for a coronavirus disease 2019 vaccine (authorized or investigational) study are allowed.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the study treatment period any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to undergo a washout at least 2 weeks prior to randomization
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.
8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening are permitted. Paracetamol/acetaminophen for analgesia will be allowed.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >9.0%), or laboratory evidence of diabetes during screening (HbA1c ≥7.0%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening
16. Has known human immunodeficiency virus or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization
25. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
26. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
28. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

29. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
30. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
31. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

32. Third shift or night shift workers
33. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
34. Placed in an institution on the basis of an official or court order

4.3. Removal from Study Drug or Assessment

Patients are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion
- AE
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (except study drug administration) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents. If a patient still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Before Amendment 6, patients who entered the DB Extension period continued their current blinded dosing regimen from the DB period. Upon implementation of Amendment 6, patients in the 12-month DB period will continue their planned dosing and assessments through the end of the 12-month DB period but will not be eligible to enter the DB Extension period and receive a dose of study drug at Month 12. For patients in the DB Extension period, patients will receive their last dose of study drug if their next visit is at Month 15, 21, 27, or 33. Patients will not receive study drug at other visits in the DB Extension period.

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. If an alternative cause is found, provide appropriate care.
   c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

Transaminase Level	Action
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.7. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.8. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that study drug complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure should be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should promptly be evaluated at the clinical study site or another hospital setting. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure (eg, supine to standing).
- The Investigator should consider downtitration, interruption, or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <90 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <100 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.
- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated, interrupted, or discontinued per Investigator judgement.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.
- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe hypertension (office SBP ≥180 mmHg and/or office DBP ≥120 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. • If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic:</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent

Study Period	Intervention
	– Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)
Month 6 to End of Study	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, prior oral antihypertensive may be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM. • Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypotension
  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction
- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, look for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.
- If a patient is on additional oral antihypertensive agents, the Investigator should consider whether these agents should be interrupted, especially during intercurrent illness or volume depletion

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ >5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia[a]. Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains >5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption or delay of study drug, according to Investigator medical judgment • Apply all measures outlined for serum K^+ >5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer or ZS-9 will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening and during the study treatment period are allowed. Occasional use of other over-the-counter systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and for at least 2 days prior to ABPM and office blood pressure measurements, and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients receiving SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin) should be on a stable dose for at least 30 days prior to screening and during the study treatment period. These medications should not be initiated or discontinued, if possible, during the study treatment period.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, oral antihypertensive medications may also be added per Investigator judgment for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study treatment period (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- Prescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi therapeutic (other than ALN-AGT01)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride), unless individually approved by both the Investigator and the Medical Monitor.
- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.

- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral oophorectomy, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests and from any exercise for 30 minutes prior to office blood pressure measurements.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the study manuals.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs (including blood pressure assessments) and weight (at the discretion of the Investigator). See further details in Section 10.2.

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed (in paper or electronic format per local regulations and institutional standards) by the patient before the screening procedures are initiated. All patients will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 2 to 4 weeks of washout (as applicable) and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once if the first screening ABPM is invalid. A valid screening ABPM recording must be obtained within 2 weeks prior to randomization for all patients. In circumstances where it is not possible to randomize an eligible patient within the 2-week window following a valid screening ABPM result that met the inclusion criterion, a single additional ABPM assessment is permitted, with no option for retesting in case of an invalid reading. Eligibility is assessed by the most recent ABPM result obtained. If a valid ABPM reading that meets the inclusion criterion is unable to be obtained within 2 weeks prior to randomization, the patient is a screen failure.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 2 to 4 weeks (as applicable) must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. To establish baseline, 3 recordings should be collected during the last week immediately prior to randomization.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the ABPM Investigator Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication.

Validity will be assessed for all ABPMs. If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording.

In circumstances where it is not possible to randomize a patient within the 2-week window following a valid ABPM recording that met the inclusion criterion, a single additional ABPM recording is permitted, with no option for retesting in case of an invalid recording. Eligibility is assessed by the most recent ABPM recording obtained. If a valid ABPM recording that meets the inclusion criterion is unable to be obtained within 2 weeks prior to randomization, the patient is a screen failure.

See further details in Section 10.1 and the ABPM Investigator Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the HBPM and OBPM Investigator Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the HBPM and OBPM Investigator Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Up to 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained during the last 2 to 4 weeks before Day 1. The second period of assessment should be obtained 2 to 4 weeks prior to the Month 3 visit. Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Biobeat Investigator Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study

drug dosing (on other days). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using validated assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide clinical management and will not be shared with sites until after the last patient completes Month 12. If clinical circumstances arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include office blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for approximately 5 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, forehead, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status (see the Recommended Neurological Assessments for All Physical Examinations document for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to

determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection for RAAS biomarkers (renin, aldosterone, and Ang I/II) occur at the same visit, and where feasible, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting plasma glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM	Parvovirus B19 DNA – quantitative
HAV antibody IgM	HHV-6 DNA viral load – quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All laboratory assessments will be measured in a central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

  An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee immediately and no later than 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Immediately and no later than 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence

will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response signal in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

For the primary analysis for the 6-month placebo-controlled DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All ALN-AGT01 Treated Set will be used to summarize the efficacy and safety of ALN-AGT01 throughout the entire DB period (including DB Extension period).

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM. The hypothesis of the dose response signal for the primary endpoint across ALN-AGT01 doses and placebo will be tested using Dunnett's procedure based on mixed model for repeated measurements (MMRM). The MMRM model will include treatment, visit, treatment-by-visit interaction, and race (black; all other races) as fixed factors and baseline 24-hour mean SBP assessed by ABPM as a covariate. An unstructured covariance matrix will be used.

The key secondary endpoints are:

- Change from baseline at Month 3 in office SBP
- Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM
- Change from baseline at Month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, and clinical laboratory assessments. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent (in paper or electronic format per local regulations and institutional standards) must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the ABPM Investigator Manual and the HBPM and OBPM Investigator Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the ABPM Investigator Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. During screening, ABPM recording must be obtained within 2 weeks prior to randomization. ABPM recordings that are associated with dosing visits after Day 1 must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording within 7 days from the end time of the invalid ABPM.

In circumstances where it is not possible to randomize a patient within the 2-week window following a valid ABPM recording that met the inclusion criterion, a single additional ABPM recording is permitted, with no option for retesting in case of an invalid recording. Eligibility is

assessed by the most recent ABPM recording obtained. If a valid ABPM recording that meets the inclusion criterion is unable to be obtained within 2 weeks prior to randomization, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medication, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the HBPM and OBPM Investigator Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.

- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel who will bring an office blood pressure instrument to the patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the HBPM and OBPM Investigator Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient should measure HBPM during the week (with at least 3 successful readings) immediately prior to randomization.

After Day 1, HBPM should be measured at least once per week. Patients may select the day of the week that is most convenient for their personal schedule. The frequency of HBPM may be increased in some patients, per Investigator discretion, if more frequent measurement is warranted (eg, during screening if patients are undergoing washout and during the temporary hold of oral antihypertensives performed from Month 5 to Month 6).

10.2. Procedures for Optional Home Healthcare Visits

Home healthcare may be allowed where applicable country and local regulations and infrastructure for home healthcare allow and will follow procedures that are in compliance with relevant local regulations and guidelines (eg, General Data Protection Regulation [EU (European Union) no 2016/679], ICH E6[R2], and the Declaration of Helsinki). The use of home healthcare is optional and will not be utilized for visits at which study drug is administered or at visits that are required to be performed at the site (see Table 1).

The option for home healthcare aims to improve patient diversity, participation, engagement, and retention in the study by reducing patient burden and minimizing study-related travel to the site, allowing flexibility in the study visit schedule.

For clinical study sites where home healthcare is utilized, the Investigator will retain responsibility for oversight, patient safety, and conduct of the trial, and will be responsible for reviewing the qualifications of and approving each home healthcare professional, delegating responsibilities to the home healthcare professional in the site delegation log, providing

instructions for home healthcare visits, communicating with the home healthcare professional at home visits as needed, and reviewing the source data files collected during the home healthcare visit. The home healthcare professional will be trained on the protocol and other relevant study documents and procedures and will be responsible for conducting vital sign assessments (including blood pressure assessments), collecting blood and urine samples, collecting weight, and documenting and notifying the site study team of any suspected or potential AE symptoms or changes to concomitant medications. The home healthcare professional will be responsible for providing source documentation of the visit to the study site.

CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 04 NOVEMBER 2022

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01 (zilebesiran)
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021 Amendment 1, 20 April 2021 Amendment 2, 09 June 2021 Amendment 3, 09 December 2021 Amendment 4, 22 March 2022 Amendment 5, 04 November 2022
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted], MD [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document as Alnylam Executive Leadership Member
Signing Time: 07-Nov-2022 | 1:29 PM EST
06848DA7D4CE4DF8B4902C2A88D6C2FD

[redacted], MD, PhD
[redacted]
Alnylam Pharmaceuticals, Inc.

07-Nov-2022 | 1:30 PM EST

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01 (zilebesiran)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 150 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM • Change from baseline at Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6 Other Secondary Endpoints • Time-adjusted change from baseline in 24-hour mean SBP and DBP, assessed by ABPM

Objectives	Endpoints
	• Change from baseline in 24-hour mean DBP, assessed by ABPM • Change from baseline in office SBP and DBP • Change in serum AGT • Change in daytime and nighttime blood pressure (including dipping pattern)
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM control and response rates • Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in pulse pressure assessed by ABPM and office blood pressure
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements

Objectives	Endpoints
• To assess the long-term treatment effect of ALN-AGT01 (through Month 36)	• Change from baseline in SBP and DBP assessed by office blood pressure and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers). Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study is open and then transition.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive, at time of initial informed consent) with untreated hypertension or on stable therapy with up to 2 antihypertensive medications. Patients

should have a daytime mean systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period and DB Extension period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 36 months. The estimated total time on study for each patient is up to 47 months, including up to 2 months of screening, followed by up to 36 months of treatment, and up to 12 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response signal in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.

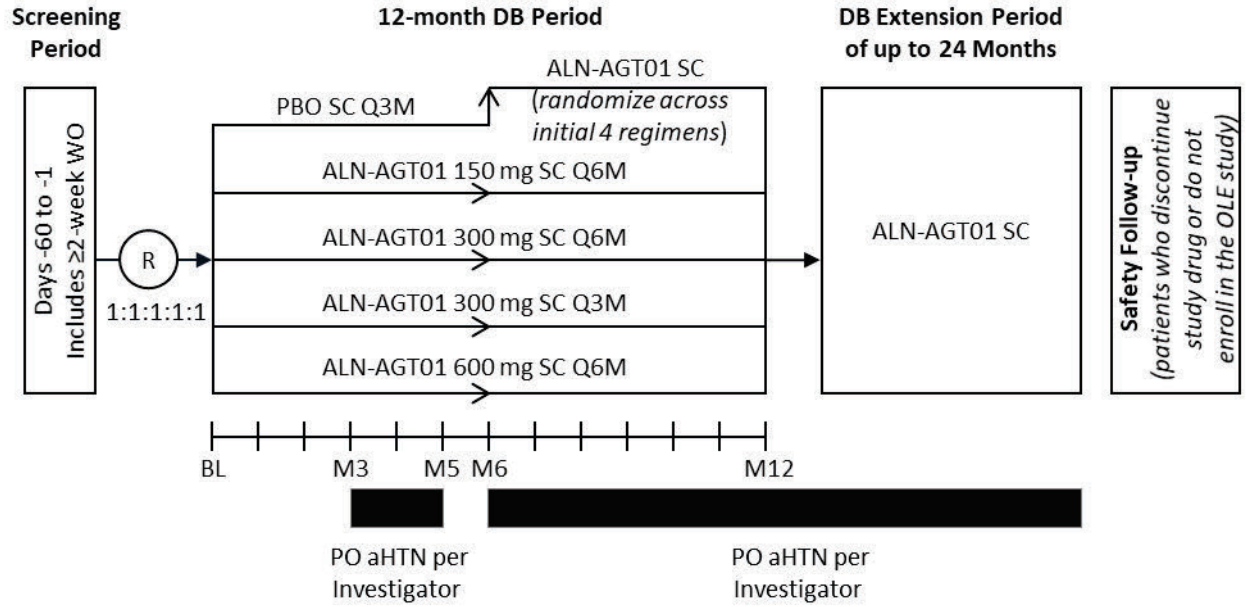
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

For the primary analysis for the 6-month placebo-controlled DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All ALN-AGT01 Treated Set will be used to summarize the efficacy and safety of ALN-AGT01 throughout the entire DB period (including DB extension period).

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.
Note: Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, 24, 30, or 36 (whichever visit occurs first).
Note: Patients who were previously taking antihypertensives at screening should undergo a washout of these medications for at least 2 weeks during the Screening period (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																
Study Visit		**Screening Period**	**Double-blind Period[a]**													**DB Extension Period[a]**	**M36/EOT/ET**	**Safety Follow-up**
				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	D1009±14	±14
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 2 to 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Section 6.2	X			X		X			X		X		X	X		X[g]	
HBPM[c,f]	Section 6.2	X	At least once per week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																
Study Visit		**Screening Period**	**Double-blind Period[a]**													**DB Extension Period[a]**	**M36/EOT/ET**	**Safety Follow-up**
				W2	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M6.5**	**M7**	**M8**	**M9**	**M12**			**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-60 to -1**	**D1**	**D15±2**	**D29 ±2**	**D57 ±7**	**D85 ±7**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D183 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D337±7**	**Q3M ±14**	**D1009±14**	**±14**
Neurological evaluation and symptom-directed physical exam	Section 6.5.3						X			X				X		X		X
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X					X	X[h]	X	

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site															
Study Visit		**Screening Period**	**Double-blind Period[a]**												**DB Extension Period[a]**	**M36/EOT/ET**	**Safety Follow-up**
				W2	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M6.5**	**M7**	**M8**	**M9**	**M12**			**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-60 to -1**	**D1**	**D15±2**	**D29 ±2**	**D57 ±7**	**D85 ±7**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D183 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D337±7**	**Q3M ±14**	**D1009±14**	**±14**
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)[i]	Section 6.5.5.2		X				X			X				X	X	X	X	X
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: renin and aldosterone	Section 6.3		X	X	X	X	X			X					X		X[g]	
RAAS biomarkers: AngI/II	Section 6.3		X				X			X					X			
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																
Study Visit		**Screening Period**	**Double-blind Period[a]**													**DB Extension Period[a]**	**M36/EOT/ET**	**Safety Follow-up**
				W2	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M6.5**	**M7**	**M8**	**M9**	**M12**			**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-60 to -1**	**D1**	**D15±2**	**D29 ±2**	**D57 ±7**	**D85 ±7**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D183 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D337±7**	**Q3M ±14**	**D1009±14**	**±14**
Study drug administration	Section 5.2.2		X				X			X				X	X	X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous																
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DB=double-blind; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAAS biomarkers (renin and aldosterone, and AngI/II) should be performed before physical examinations and 12-lead ECGs.
- Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may receive a dose of ALN-AGT01 at the Month 12 visit and continue their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, 24, 30, or 36 (whichever visit occurs first). Patients who rollover at Month 12 should complete all assessments scheduled for the Month 12 visit except for study drug administration. Patients who rollover at Months 18, 24, 30, or 36 should complete the EOT visit instead of the assessments scheduled at those visits.
- Patients who do not enroll in the OLE study will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator.

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																
			Double-blind Period[a]													DB Extension Period[a]	M36/EOT/ET	Safety Follow-up
Study Visit		**Screening Period**		**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M6.5**	**M7**	**M8**	**M9**	**M12**			**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-60 to -1**	**D1**	**D15±2**	**D29 ±2**	**D57 ±7**	**D85 ±7**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D183 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D337±7**	**Q3M ±14**	**D1009±14**	**±14**

- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 2 weeks of washout (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.

[e] ABPM recordings associated with dosing visits must be obtained within 2 weeks prior to randomization and within 7 days before dosing visits after Day 1 and results reviewed before dosing.

[f] HBPM should be measured at least once per week in the morning upon waking. HBPM may be measured more frequently in some patients, per Investigator discretion, if more frequent measurement is warranted (eg, during screening if patients are undergoing washout and between Months 5 and 6 if oral antihypertensives are temporarily held). HBPM is not required at times when ABPM is being assessed.

[g] ABPM and collection of RAAS biomarkers should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12, and ABPM should only be performed at ET if the patient and has not had an ABPM within the last 3 months. These assessments should not be performed at Month 36.

[h] Fasting plasma laboratory samples should only be collected at Month 18.

[i] The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
LFT	Liver function test
MAO	Monoamine oxidase
MMRM	Mixed model for repeated measurements
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal
ZS-9	Sodium zirconium cyclosilicate

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01 (zilebesiran), a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock and Krousel-Wood 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension

and to overcome the limitations of current therapies is a key unmet need.[Dzau and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease

population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM • Change from baseline at Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6 Other Secondary Endpoints • Time-adjusted change from baseline in 24-hour mean SBP and DBP, assessed by ABPM

Objectives	Endpoints
	• Change from baseline in 24-hour mean DBP, assessed by ABPM • Change from baseline in office SBP and DBP • Change in serum AGT • Change in daytime and nighttime blood pressure (including dipping pattern)
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM control and response rates • Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in pulse pressure assessed by ABPM and office blood pressure
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements

Objectives	Endpoints
• To assess the long-term treatment effect of ALN-AGT01 (through Month 36)	• Change from baseline in SBP and DBP assessed by office blood pressure and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers [CCBs]).

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, home blood pressure

monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM).[Williams 2018] Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 24 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, 24, 30, or 36 (whichever visit occurs first).

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the separate ALN-AGT01 OLE study will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or until 12 months after their last dose of study drug, whichever comes earlier. During the Safety Follow-up period, patients should return to their pre-study medical care (usual care).

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 36 months. The estimated total time on study for each patient is up to 47 months, including up to 2 months of screening, followed by up to 36 months of treatment, and up to 12 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for 2 to 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe hypertension (office SBP ≥180 mmHg or DBP ≥120 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a CCB and/or thiazide/thiazide-like diuretic may be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 2 to 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer (or with sodium zirconium cyclosilicate [ZS-9]), if available, for treatment of potential hyperkalemia.[Georgianos and Agarwal 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative

effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. During the course of the study, serum AGT, plasma PK, and treatment assignment using dummy IDs will be made available to a small, independent pharmacometrics team at the Sponsor that will not be involved in the conduct or oversight of the study. After the last patient completes the Month 3 visit and prior to the last patient's Month 6 visit, a limited amount (ie, one-third) of SBP data will be made available to this small, independent pharmacometrics team for preliminary PK/PD modeling. After the database lock to support the analysis of Month 6 data is complete, all other Sponsor personnel will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after the analysis of

Month 12 data is complete. The Sponsor and all site personnel will be blinded to serum AGT results until their respective unblinding. Serum AGT results will not be reported to site personnel until the last patient completes the assessments at the Month 12 visit.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 12 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the OLE study.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive, at time of initial informed consent
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with up to 2 antihypertensive medications. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Daytime mean SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to this ABPM (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics [eg, chlorthalidone] or CCBs [eg, amlodipine]).

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension (including, but not limited to, renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, aortic coarctation, or due to known history of moderate-to-severe obstructive sleep apnea not treated with continuous positive airway pressure therapy)
2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 2 to 4 weeks of washout:
    a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
    b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)

d. Elevated potassium >5 mEq/L
e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational. Patients who are in follow-up for a coronavirus disease 2019 vaccine (authorized or investigational) study are allowed.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the study treatment period any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to undergo a washout at least 2 weeks prior to randomization
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.
8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening are permitted. Paracetamol/acetaminophen for analgesia will be allowed.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >9.0%), or laboratory evidence of diabetes during screening (HbA1c ≥7.0%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening

16. Has known human immunodeficiency virus or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization
25. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
26. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
28. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

29. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
30. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
31. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

32. Third shift or night shift workers

33. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
34. Placed in an institution on the basis of an official or court order

4.3. Removal from Study Drug or Assessment

Patients are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion
- AE
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review

of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (except study drug administration) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents. If a patient still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.

- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period. Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be

masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
    a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
    b. If an alternative cause is found, provide appropriate care.
    c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.7. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.8. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that study drug complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure should be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should promptly be evaluated at the clinical study site or another hospital setting. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure (eg, supine to standing).
- The Investigator should consider downtitration, interruption, or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <90 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <100 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.
- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated, interrupted, or discontinued per Investigator judgement.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.

- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe hypertension (office SBP ≥180 mmHg and/or office DBP ≥120 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. • If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	Intervene if clinically significant blood pressure elevation: • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.

Study Period	Intervention
Months 3 to 6	Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic: • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent – Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)
Month 6 to End of Study	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, prior oral antihypertensive may be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM. • Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypotension

  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction

- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, look for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.
- If a patient is on additional oral antihypertensive agents, the Investigator should consider whether these agents should be interrupted, especially during intercurrent illness or volume depletion

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ >5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia[a]. Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains >5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption or delay of study drug, according to Investigator medical judgment • Apply all measures outlined for serum K^+ >5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.
[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer or ZS-9 will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all

prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening and during the study treatment period are allowed. Occasional use of other over-the-counter systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and for at least 2 days prior to ABPM and office blood pressure measurements, and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients receiving SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin) should be on a stable dose for at least 30 days prior to screening and during the study treatment period. These medications should not be initiated or discontinued, if possible, during the study treatment period.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, oral antihypertensive medications may also be added per Investigator judgment for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study treatment period (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- Prescription NSAIDs

- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi therapeutic (other than ALN-AGT01)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride), unless individually approved by both the Investigator and the Medical Monitor.
- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.

- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral oophorectomy, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests and from any exercise for 30 minutes prior to office blood pressure measurements.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the study manuals.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs (including blood pressure assessments) and weight (at the discretion of the Investigator). See further details in Section 10.2.

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed (in paper or electronic format per local regulations and institutional standards) by the patient before the screening procedures are initiated. All patients will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 2 to 4 weeks of washout (as applicable) and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once if the first screening ABPM is invalid. A valid screening ABPM recording must be obtained within 2 weeks prior to randomization for all patients. In circumstances where it is not possible to randomize an eligible patient within the 2-week window following a valid screening ABPM result that met the inclusion criterion, a single additional ABPM assessment is permitted, with no option for retesting in case of an invalid reading. Eligibility is assessed by the most recent

ABPM result obtained. If a valid ABPM reading that meets the inclusion criterion is unable to be obtained within 2 weeks prior to randomization, the patient is a screen failure.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 2 to 4 weeks (as applicable) must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. To establish baseline, 3 recordings should be collected during the last week immediately prior to randomization.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the ABPM Investigator Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute “remote visit blood pressure measurement” may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication.

Validity will be assessed for all ABPMs. If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording.

In circumstances where it is not possible to randomize a patient within the 2-week window following a valid ABPM recording that met the inclusion criterion, a single additional ABPM recording is permitted, with no option for retesting in case of an invalid recording. Eligibility is assessed by the most recent ABPM recording obtained. If a valid ABPM recording that meets the inclusion criterion is unable to be obtained within 2 weeks prior to randomization, the patient is a screen failure.

See further details in Section 10.1 and the ABPM Investigator Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the HBPM and OBPM Investigator Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the HBPM and OBPM Investigator Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Up to 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained during the last 2 to 4 weeks before Day 1. The second period of assessment should be obtained 2 to 4 weeks prior to the Month 3 visit. Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Biobeat Investigator Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples collected for AngI and AngII require special processing and will be assessed at sites that have appropriate resources, equipment, and reagents. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide clinical management and will not be shared with sites until after the last patient completes Month 12. If clinical circumstances

arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include office blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for approximately 5 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, forehead, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the

midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status (see the Recommended Neurological Assessments for All Physical Examinations document for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection for RAAS biomarkers (renin, aldosterone, and Ang I/II) occur at the same visit, and where feasible, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting plasma glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM	Parvovirus B19 DNA – quantitative
HAV antibody IgM	HHV-6 DNA viral load – quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All laboratory assessments will be measured in a central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

  An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee immediately and no later than 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Immediately and no later than 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence

will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response signal in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

For the primary analysis for the 6-month placebo-controlled DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All ALN-AGT01 Treated Set will be used to summarize the efficacy and safety of ALN-AGT01 throughout the entire DB period (including DB extension period).

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM. The hypothesis of the dose response signal for the primary endpoint across ALN-AGT01 doses and placebo will be tested using Dunnett's procedure based on mixed model for repeated measurements (MMRM). The MMRM model will include treatment, visit, treatment-by-visit interaction, and race (black; all other races) as fixed factors and baseline 24-hour mean SBP assessed by ABPM as a covariate. An unstructured covariance matrix will be used.

The key secondary endpoints are:

- Change from baseline at Month 3 in office SBP
- Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM
- Change from baseline at Month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

The primary analysis will be conducted after all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit. No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent (in paper or electronic format per local regulations and institutional standards) must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the ABPM Investigator Manual and the HBPM and OBPM Investigator Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the ABPM Investigator Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. During screening, ABPM recording must be obtained within 2 weeks prior to randomization. ABPM recordings that are associated with dosing visits after Day 1 must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording within 7 days from the end time of the invalid ABPM.

In circumstances where it is not possible to randomize a patient within the 2-week window following a valid ABPM recording that met the inclusion criterion, a single additional ABPM recording is permitted, with no option for retesting in case of an invalid recording. Eligibility is

assessed by the most recent ABPM recording obtained. If a valid ABPM recording that meets the inclusion criterion is unable to be obtained within 2 weeks prior to randomization, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medication, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the HBPM and OBPM Investigator Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.

- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel who will bring an office blood pressure instrument to the patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the HBPM and OBPM Investigator Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient should measure HBPM during the week (with at least 3 successful readings) immediately prior to randomization.

After Day 1, HBPM should be measured at least once per week. Patients may select the day of the week that is most convenient for their personal schedule. The frequency of HBPM may be increased in some patients, per Investigator discretion, if more frequent measurement is warranted (eg, during screening if patients are undergoing washout and during the temporary hold of oral antihypertensives performed from Month 5 to Month 6).

10.2. Procedures for Optional Home Healthcare Visits

Home healthcare may be allowed where applicable country and local regulations and infrastructure for home healthcare allow and will follow procedures that are in compliance with relevant local regulations and guidelines (eg, General Data Protection Regulation [EU (European Union) no 2016/679], ICH E6[R2], and the Declaration of Helsinki). The use of home healthcare is optional and will not be utilized for visits at which study drug is administered or at visits that are required to be performed at the site (see Table 1).

The option for home healthcare aims to improve patient diversity, participation, engagement, and retention in the study by reducing patient burden and minimizing study-related travel to the site, allowing flexibility in the study visit schedule.

For clinical study sites where home healthcare is utilized, the Investigator will retain responsibility for oversight, patient safety, and conduct of the trial, and will be responsible for reviewing the qualifications of and approving each home healthcare professional, delegating responsibilities to the home healthcare professional in the site delegation log, providing

instructions for home healthcare visits, communicating with the home healthcare professional at home visits as needed, and reviewing the source data files collected during the home healthcare visit. The home healthcare professional will be trained on the protocol and other relevant study documents and procedures and will be responsible for conducting vital sign assessments (including blood pressure assessments), collecting blood and urine samples, collecting weight, and documenting and notifying the site study team of any suspected or potential AE symptoms or changes to concomitant medications. The home healthcare professional will be responsible for providing source documentation of the visit to the study site.

CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 22 MARCH 2022

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01 (zilebesiran)
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021 Amendment 1, 20 April 2021 Amendment 2, 09 June 2021 Amendment 3, 09 December 2021 Amendment 4, 22 March 2022
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SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document as Alnylam Executive Leadership Member
Signing Time: 26-Mar-2022 | 2:35 PM EDT
06848DA7D4CE4DF8B4902C2A88D6C2FD

[redacted], MD, PhD
[redacted]
Alnylam Pharmaceuticals, Inc.

26-Mar-2022 | 2:35 PM EDT

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01 (zilebesiran)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 100 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM • Change from baseline at Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6 Other Secondary Endpoints

Objectives	Endpoints
	• Time-adjusted change from baseline in 24-hour mean SBP and DBP, assessed by ABPM • Change from baseline in 24-hour mean DBP, assessed by ABPM • Change from baseline in office SBP and DBP • Change in serum AGT • Change in daytime and nighttime blood pressure (including dipping pattern)
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM control and response rates • Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in pulse pressure assessed by ABPM and office blood pressure
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive,	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements

Objectives	Endpoints
cuffless device to those obtained by standard cuff-based methods	
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by office blood pressure and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers). Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with up to 2 antihypertensive medications. Patients should have a daytime mean systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period and DB Extension period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 38 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 12 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response signal in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.

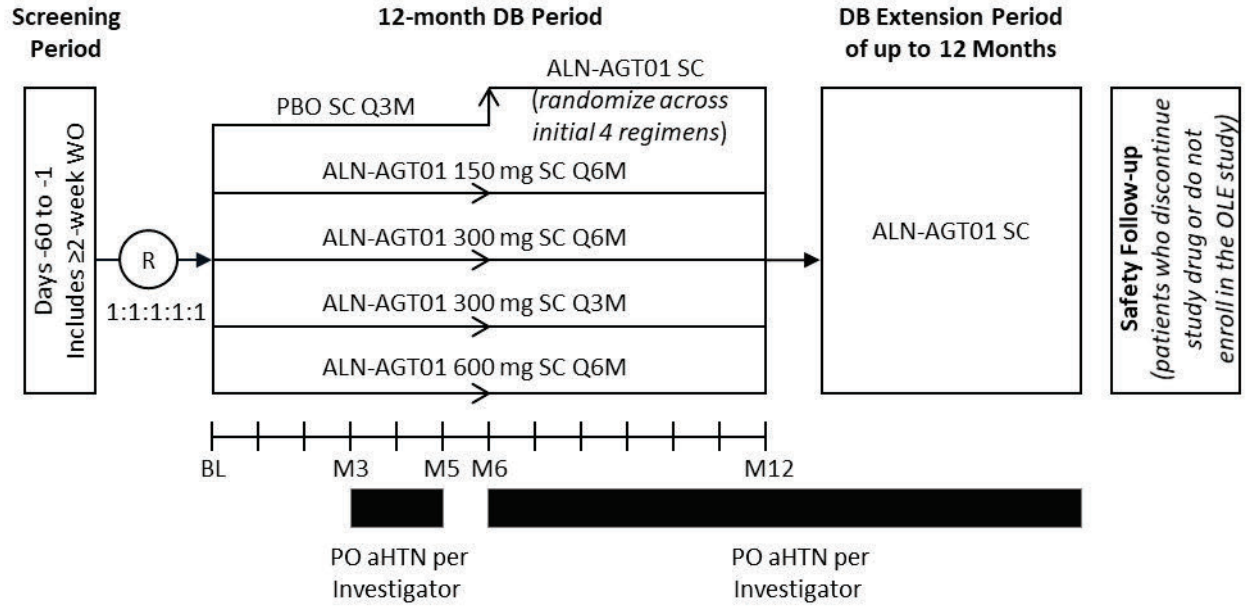
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

For the primary analysis for the 6-month placebo-controlled DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All ALN-AGT01 Treated Set will be used to summarize the efficacy and safety of ALN-AGT01 throughout the entire DB period (including DB extension period).

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.
Note: Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).
Note: Patients who were previously taking antihypertensives at screening should undergo a washout of these medications for at least 2 weeks during the Screening period (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 2 to 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Sections 6.2	X			X		X			X		X		X	X		X[g]	
HBPM[c,f]	Section 6.2	X	At least once per week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Neurological evaluation and symptom-directed physical exam	Section 6.5.3						X			X				X		X		X
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X					X	X[h]	X	
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)	Section 6.5.5.2		X				X			X				X	X	X	X	X
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: renin and aldosterone	Section 6.3		X	X	X	X	X			X					X		X[g]	
RAAS biomarkers: AngI/II	Section 6.3		X				X			X					X			
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									
Study drug administration	Section 5.2.2		X				X			X				X	X	X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF;	Continuous																

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
	record non-serious AEs after first dose of study drug																	
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DB=double-blind; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections should be performed before physical examinations and 12-lead ECGs.
- Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may receive a dose of ALN-AGT01 at the Month 12 visit and continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first). Patients who rollover at Month 12 should complete all assessments scheduled for the Month 12 visit except for study drug administration. Patients who rollover at Months 18 or 24 should complete the EOT visit instead of the assessments scheduled at those visits.
- Patients who do not enroll in the OLE study will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 2 weeks of washout (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.

[e] ABPM recordings associated with dosing visits should be obtained within 2 weeks prior to randomization and within 7 days before dosing visits after Day 1 and results reviewed before dosing.

[f] HBPM should be measured at least once per week in the morning upon waking. HBPM may be measured more frequently in some patients, per Investigator discretion, if more frequent measurement is warranted (eg, during screening if patients are undergoing washout and between Months 5 and 6 if oral antihypertensives are temporarily held). HBPM is not required at times when ABPM is being assessed.

[g] ABPM and collection of RAAS biomarkers should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12, and ABPM should only be performed at ET if the patient and has not had an ABPM within the last 3 months. These assessments should not be performed at Month 24.

[h] Fasting plasma laboratory samples should only be collected at Month 18.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
LFT	Liver function test
MAO	Monoamine oxidase
MMRM	Mixed model for repeated measurements
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal
ZS-9	Sodium zirconium cyclosilicate

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01 (zilebesiran), a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock and Krousel-Wood 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension

and to overcome the limitations of current therapies is a key unmet need.[Dzau and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease

population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM • Change from baseline at Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6 Other Secondary Endpoints

Objectives	Endpoints
	• Time-adjusted change from baseline in 24-hour mean SBP and DBP, assessed by ABPM • Change from baseline in 24-hour mean DBP, assessed by ABPM • Change from baseline in office SBP and DBP • Change in serum AGT • Change in daytime and nighttime blood pressure (including dipping pattern)
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM control and response rates • Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in pulse pressure assessed by ABPM and office blood pressure
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive,	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements

Objectives	Endpoints
cuffless device to those obtained by standard cuff-based methods	
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by office blood pressure and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers [CCBs]).

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications

may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, home blood pressure monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM).[Williams 2018] Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the separate ALN-AGT01 OLE study will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or until 12 months after their last dose of study drug, whichever comes earlier.

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 38 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 12 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for 2 to 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe hypertension (office SBP ≥180 mmHg or DBP ≥120 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a CCB and/or thiazide/thiazide-like diuretic may be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 2 to 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer (or with sodium zirconium cyclosilicate [ZS-9]), if available, for treatment of potential hyperkalemia.[Georgianos and Agarwal 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative

effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. During the course of the study, serum AGT, plasma PK, and treatment assignment using dummy IDs will be made available to a small, independent pharmacometrics team at the Sponsor that will not be involved in the conduct or oversight of the study. After the last patient completes the Month 3 visit and prior to the last patient's Month 6 visit, a limited amount (ie, one-third) of SBP data will be made available to this small, independent pharmacometrics team for preliminary PK/PD modeling. After the database lock to support the analysis of Month 6 data is complete, all other Sponsor personnel will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after the analysis of

Month 12 data is complete. The Sponsor and all site personnel will be blinded to serum AGT results until their respective unblinding. Serum AGT results will not be reported to site personnel until the last patient completes the assessments at the Month 12 visit.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 12 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the OLE study.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with up to 2 antihypertensive medications. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Daytime mean SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to this ABPM (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics [eg, chlorthalidone] or CCBs [eg, amlodipine]).

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension (including, but not limited to, renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, aortic coarctation, or due to known history of moderate-to-severe obstructive sleep apnea not treated with continuous positive airway pressure therapy)
2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 2 to 4 weeks of washout:
    a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
    b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)

d. Elevated potassium >5 mEq/L
e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational. Patients who are in follow-up for a coronavirus disease 2019 vaccine (authorized or investigational) study are allowed.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the study treatment period any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to undergo a washout at least 2 weeks prior to randomization
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.
8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening are permitted. Paracetamol/acetaminophen for analgesia will be allowed.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >9.0%), or laboratory evidence of diabetes during screening (HbA1c ≥7.0%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening

16. Has known human immunodeficiency virus or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization
25. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
26. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
28. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

29. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
30. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
31. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

32. Third shift or night shift workers

33. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion
- AE
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (except study drug administration) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.

- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period. Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be

masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
    a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
    b. If an alternative cause is found, provide appropriate care.
    c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored and refrigerated at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.7. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.8. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that study drug complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure should be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should promptly be evaluated at the clinical study site or another hospital setting. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure (eg, supine to standing).
- The Investigator should consider downtitration, interruption, or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <90 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <100 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.
- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated, interrupted, or discontinued per Investigator judgement.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.

- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe hypertension (office SBP ≥180 mmHg and/or office DBP ≥120 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. • If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	Intervene if clinically significant blood pressure elevation: • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.

Study Period	Intervention
Months 3 to 6	Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic: • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent – Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)
Month 6 to End of Study	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, prior oral antihypertensive may be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM. • Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypotension

  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction

- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, look for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.
- If a patient is on additional oral antihypertensive agents, the Investigator should consider whether these agents should be interrupted, especially during intercurrent illness or volume depletion

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ ≥5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia.[a] Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains ≥5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption or delay of study drug, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.
[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer or ZS-9 will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all

prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening and during the study treatment period are allowed. Occasional use of other over-the-counter systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and for at least 2 days prior to ABPM and office blood pressure measurements, and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients receiving SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin) should be on a stable dose for at least 30 days prior to screening and during the study treatment period. These medications should not be initiated or discontinued, if possible, during the study treatment period.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, oral antihypertensive medications may also be added per Investigator judgment for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study treatment period (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- Prescription NSAIDs

- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi therapeutic (other than ALN-AGT01)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride).
- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.

- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral oophorectomy, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests and from any exercise for 30 minutes prior to office blood pressure measurements.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the Study Manuals.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs and weight (at the discretion of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed (in paper or electronic format per local regulations and institutional standards) by the patient or legal guardian before the screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 2 to 4 weeks of washout (as applicable) and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to

return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 2 to 4 weeks (as applicable) must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. To establish baseline, 3 recordings should be collected during the last week immediately prior to randomization.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication.

Validity will be assessed for all ABPMs. If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording. If the second ABPM recording is also invalid during screening, the patient is a screen failure.

See further details in Section 10.1 and the Study Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Up to 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained during the last 2 to 4 weeks before Day 1. Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Study Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples collected for AngI and AngII require special processing and will be assessed at sites that have appropriate resources, equipment, and reagents. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide clinical management and will not be shared with sites until after the last patient completes Month 12. If clinical circumstances arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for approximately 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the

average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status (see the Study Manual for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed according to the Study Manual during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection occur at the same visit, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as

indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)

Coagulation	
Prothrombin time Partial thromboplastin time	International normalized ratio
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting plasma glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are

not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM	Parvovirus B19 DNA – quantitative
HAV antibody IgM	HHV-6 DNA viral load – quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All laboratory assessments will be measured in a central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

  An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious adverse events must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence

will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response signal in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

For the primary analysis for the 6-month placebo-controlled DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All ALN-AGT01 Treated Set will be used to summarize the efficacy and safety of ALN-AGT01 throughout the entire DB period (including DB extension period).

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM. The hypothesis of the dose response signal for the primary endpoint across ALN-AGT01 doses and placebo will be tested using Dunnett's procedure based on mixed model for repeated measurements (MMRM). The MMRM model will include treatment, visit, treatment-by-visit interaction, and race (black; all other races) as fixed factors and baseline 24-hour mean SBP assessed by ABPM as a covariate. An unstructured covariance matrix will be used.

The key secondary endpoints are:

- Change from baseline at Month 3 in office SBP
- Change from baseline at Month 6 in 24-hour mean SBP assessed by ABPM
- Change from baseline at Month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications at Month 6

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

The primary analysis will be conducted after all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit. No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent (in paper or electronic format per local regulations and institutional standards) must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the Study Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. During screening, ABPM recording should be obtained within 2 weeks prior to randomization. ABPM recordings that are associated with dosing visits after Day 1 must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording within 4 days. If the second ABPM recording is also invalid during screening, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medication, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.

- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel who will bring an office blood pressure instrument to the patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient should measure HBPM during the week (with at least 3 successful readings) immediately prior to randomization.

After Day 1, HBPM should be measured at least once per week. Patients may select the day of the week that is most convenient for their personal schedule. The frequency of HBPM may be increased in some patients, per Investigator discretion, if more frequent measurement is warranted (eg, during screening if patients are undergoing washout and during the temporary hold of oral antihypertensives performed from Month 5 to Month 6).

CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 09 DECEMBER 2021

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01 (zilebesiran)
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021 Amendment 1, 20 April 2021 Amendment 2, 09 June 2021 Amendment 3, 09 December 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted], MD, PhD [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

[redacted] MD, PhD

[redacted]

Alnylam Pharmaceuticals, Inc.

9 Dec, 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01 (zilebesiran)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 100 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic

of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers). Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by daily home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with 1 or more antihypertensive medications. Patients should have a daytime mean systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period and DB Extension period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 38 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 12 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

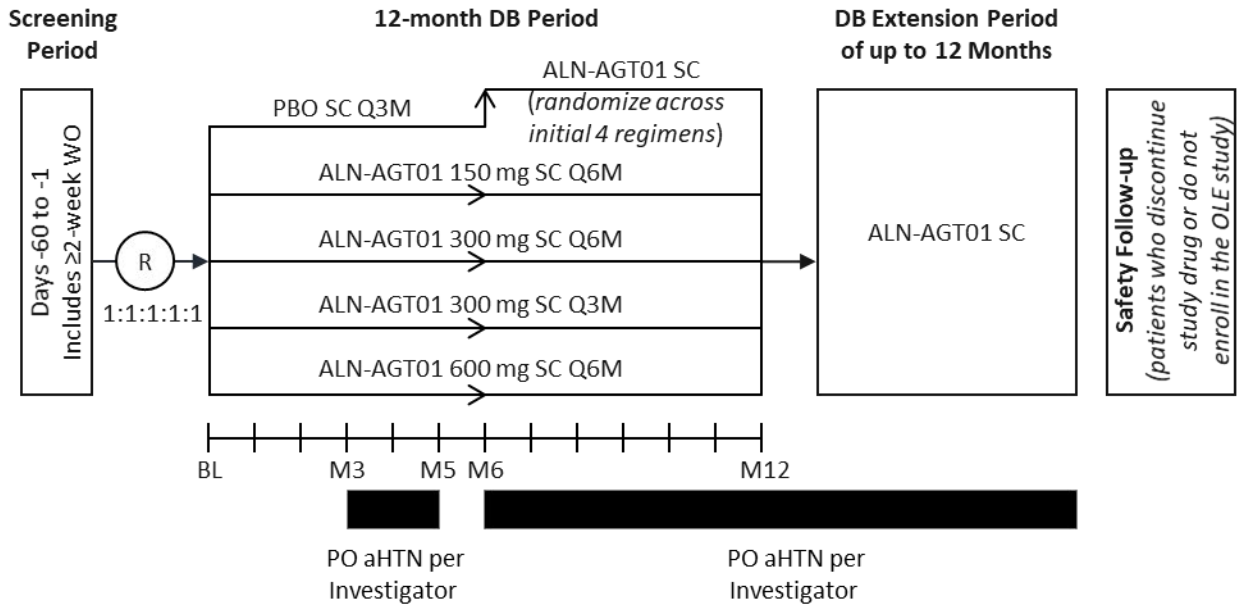
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.
Note: Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).
Note: Patients who were previously taking antihypertensives at screening should undergo a washout of these medications for at least 2 weeks during the Screening period (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 2 to 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Sections 6.2	X			X		X			X		X		X	X	X	X	X
HBPM[c,f]	Section 6.2	X	At least 3 times/week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	

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Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
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Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Neurological evaluation and symptom-directed physical exam	Section 6.5.3						X			X				X		X		X
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
24-hour urine for aldosterone, sodium, and creatinine	Sections 6.5.5 and 6.6	X					X			X					X			
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X				X	X	X	X	X

Table 1: Schedule of Assessments

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Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)	Section 6.5.5.2		X				X			X				X	X	X	X	X
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: renin and aldosterone	Section 6.3		X	X	X	X	X			X					X	X	X	
RAAS biomarkers: AngI/II	Section 6.3		X				X			X					X			
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	X
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									
Study drug administration	Section 5.2.2		X				X			X				X	X	X		

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous																
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections should be performed before physical examinations and 12-lead ECGs.
- Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may receive a dose of ALN-AGT01 at the Month 12 visit and continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first). Patients who rollover at Month 12 should complete all assessments scheduled for the Month 12 visit except for study drug administration. Patients who rollover at Months 18 or 24 should complete the EOT visit instead of the assessments scheduled at those visits.
- Patients who do not enroll in the OLE study will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14

- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 2 weeks of washout (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers).

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.

[e] ABPM recordings associated with dosing visits should be obtained within 7 days before the dosing visit and results reviewed before dosing. ABPM should only be collected at Months 18 and 24 for patients in the DB Extension period.

[f] HBPM should be measured in the morning upon waking. HBPM should be measured daily between Months 5 and 6 if oral antihypertensives are temporarily held. HBPM is not required at times when ABPM is being assessed.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour:minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction

Abbreviation	Definition
LFT	Liver function test
MAO	Monoamine oxidase
MCP-Mod	Multiple comparison-modeling
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal
ZS-9	Sodium zirconium cyclosilicate

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01 (zilebesiran), a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock and Krousel-Wood 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension

and to overcome the limitations of current therapies is a key unmet need.[Dzau and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease

population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 2 weeks (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or calcium channel blockers [CCBs]).

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, home blood pressure monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM). Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the separate ALN-AGT01 OLE study will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or until 12 months after their last dose of study drug, whichever comes earlier.

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 38 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 12 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for 2 to 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual

modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe hypertension (office SBP ≥180 mmHg or DBP ≥120 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a CCB and/or thiazide/thiazide-like diuretic will be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 2 to 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by daily HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer (or with sodium zirconium cyclosilicate [ZS-9]), if available, for treatment of potential hyperkalemia.[Georgianos and Agarwal 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events

(patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months

- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. After the last patient completes the Month 3 visit and prior to the last patient's Month 6 visit, serum AGT, PK, and a limited amount (ie, one-third) of SBP data and treatment assignment using dummy IDs will be made available to a small, independent pharmacometrics team at the Sponsor that will not be involved in the conduct or oversight of the study. After the database lock to support the analysis of Month 6 data is complete, all other Sponsor personnel will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after the analysis of Month 12 data is complete. The Sponsor and all site personnel will be blinded to serum AGT results until their respective unblinding. Serum AGT results will not be reported to site personnel until the last patient completes the assessments at the Month 12 visit.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people

on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 12 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the OLE study.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with 1 or more antihypertensive medications. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Daytime mean SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to this ABPM (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics [eg, chlorthalidone] or CCBs [eg, amlodipine]).

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension
2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 2 to 4 weeks of washout:
   a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
   b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
   c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
   d. Elevated potassium >5 mEq/L
   e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the study treatment period any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to undergo a washout at least 2 weeks prior to randomization
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.

8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening are permitted. Paracetamol/acetaminophen for analgesia will be allowed.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.0%), newly diagnosed Type 2 diabetes mellitus (within 6 months prior to randomization), or laboratory evidence of diabetes during screening (fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], random plasma glucose ≥200 mg/dL [11.1 mmol/L], or HbA1c ≥6.5%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening
16. Has known human immunodeficiency virus or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization

25. Known change in body weight >10% in last 6 months prior to screening
26. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
27. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
29. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
31. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
32. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

33. Third shift or night shift workers
34. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
35. Unable or unwilling to perform HBPM as specified

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion

- AE
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (except study drug administration) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period. Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. If an alternative cause is found, provide appropriate care.
   c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

Transaminase Level	Action
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored and refrigerated at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.7. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.8. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that study drug complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure will be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should promptly be evaluated at the clinical study site or another hospital setting. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure (eg, supine to standing).
- The Investigator should consider downtitration, interruption, or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <90 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <100 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.
- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated, interrupted, or discontinued per Investigator judgement.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.
- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe hypertension (office SBP ≥180 mmHg and/or office DBP ≥120 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. • If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic:</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic should be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent

Study Period	Intervention
	– Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)
Month 6 to End of Study	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, prior oral antihypertensive should be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM. • Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypotension
  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction
- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, look for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.
- If a patient is on additional oral antihypertensive agents, the Investigator should consider whether these agents should be interrupted, especially during intercurrent illness or volume depletion

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ ≥5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia.[a] Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains ≥5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption or delay of study drug, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer or ZS-9 will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening and during the study treatment period are allowed. Occasional use of other over-the-counter systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and for at least 7 days prior to ABPM and office blood pressure measurements, and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients receiving SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin) should be on a stable dose for at least 30 days prior to screening and during the study treatment period. These medications should not be initiated or discontinued, if possible, during the study treatment period.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, Investigators will titrate therapy with oral antihypertensives to a target blood pressure range (office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg). All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study treatment period (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- Prescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi therapeutic (other than ALN-AGT01)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride).
- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).

- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018

European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs and weight (at the discretion of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed (in paper or electronic format per local regulations and institutional standards) by the patient or legal guardian before the screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 2 to 4 weeks of washout (as applicable) and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once as described in Section 6.2.1, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to

return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 2 to 4 weeks (as applicable) must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. HBPM must be collected after at least 2 to 4 weeks of washout (as applicable) for at least 2 consecutive weeks (at least 3 recordings per week) prior to randomization to establish baseline.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication.

Adequacy will be assessed for all ABPMs. If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

See further details in Section 10.1 and the Study Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Approximately 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained after at least 2 to 4 weeks of washout (as applicable). Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Study Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples collected for AngI and AngII require special processing and will be assessed at sites that have appropriate resources, equipment, and reagents. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Levels of aldosterone will also be analyzed in urine collections at the time points listed in the Schedule of Assessments (Table 1). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide clinical management and will not be shared with sites until after the last patient completes Month 12. If clinical circumstances arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for approximately 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the

average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status (see the Study Manual for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed according to the Study Manual during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection occur at the same visit, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as

indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning. A 24-hour urine collection for aldosterone, sodium, and creatinine will be performed at time points listed in the Schedule of Assessments (Table 1). These 24-hour collections should be obtained within 2 days before the ABPM associated with the same visit.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen

Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting plasma glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per

the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and IgG	Parvovirus B19 DNA – quantitative
HAV antibody IgM	HHV-6 DNA viral load – quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen

Note:

- All laboratory assessments will be measured in a central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

  An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as

may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. ‘Severity’ characterizes the intensity of an AE. ‘Serious’ is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the study drug?” A “yes” response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient’s health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications,

or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event

- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious adverse events must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). In addition to the dedicated collections for optional exploratory biomarkers (urine, plasma, serum), aliquots from each 24-hour urine collection will be archived for potential exploratory investigations. These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05. Table 8 shows the statistical power with various standard deviation assumptions.

Table 8: Statistical Power to Detect 10 mmHg Difference Between ALN-AGT01 and Placebo With Various Standard Deviation Assumptions

Assumption of Standard Deviation (mmHg)	Statistical Power to Detect Dose Response Trend (%)	Statistical Power to Detect Difference Between an Individual ALN-AGT01 Dose Versus Placebo (%)
15	97	96
18	90	88
20	84	80

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of ALN-AGT01 and have at least 1 nonmissing postdose PK assessment.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All ALN-AGT01 Treated Set:** All patients who received any amount of 1 of the 4 ALN-AGT01 dosing regimens, including patients who took ALN-AGT01 during the 6-month placebo-controlled period and patients who initially took placebo and then switched to ALN-AGT01 after the Month 6 visit.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change in SBP from baseline at Month 3 assessed by ABPM. The primary hypothesis of the dose response relationship for the primary endpoint across ALN-AGT01 doses and placebo will be tested using a multiple comparison– modeling (MCP Mod) approach.[Bretz 2005] The presence of a dose-response trend will be initially tested against a set of prespecified dose-response models at a 2-sided significance level of 0.05, adjusted for multiplicity (the MCP step). Several candidate models will be prespecified in the

SAP. Then, the dose-response curves will be further estimated (the modeling step) based on the 'best' fitted dose response model. Furthermore, each ALN-AGT01 dose group will be compared against placebo using Dunnett's Test.

For the secondary endpoints of change in DBP assessed by ABPM at Month 3 and change in SBP and DBP assessed by ABPM at Month 6, each ALN-AGT01 dose group will be compared with placebo. For change in office SBP and DBP, each ALN-AGT01 dose group will be compared with placebo at Month 3 and Month 6 and also using the time-adjusted average from Month 1 to Month 3 and from Month 1 to Month 6.

No multiplicity adjustment is applied across primary and secondary endpoints.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT

for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

The primary analysis will be conducted after all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit. No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent (in paper or electronic format per local regulations and institutional standards) must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the Study Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with adequacy assessment. An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 4 days. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medication, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other

appropriately trained personnel who will bring an office blood pressure instrument to the patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM every morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient must measure HBPM for at least 2 consecutive weeks (and with at least 3 successful readings per week) prior to randomization. Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to collecting these baseline HBPM measurements (4 weeks of washout is required for long-acting antihypertensive medications, such as long-acting diuretics or CCBs). If adequate baseline HBPM data (at least 3 successful readings per week for at least 2 consecutive weeks) are not collected within the Screening period, the patient is a screen failure.

After Day 1, HBPM should be measured at least 3 times per week. Patients may select the 3 days of the week that are most convenient for their personal schedule. The frequency of HBPM monitoring should be increased to daily during the temporary hold of oral antihypertensives performed in some patients from Month 5 to Month 6.

CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 09 JUNE 2021

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021 Amendment 1, 20 April 2021 Amendment 2, 09 June 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted], MD [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted], MD, PhD

[redacted]

Alnylam Pharmaceuticals, Inc.

June 9, 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 50 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM and response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic

of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 4 weeks. Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by daily home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with 1 or more antihypertensive medications of the following classes: an angiotensin converting enzyme inhibitor, angiotensin II-receptor blocker, renin inhibitor, calcium channel blocker, thiazide diuretic, and/or thiazide-like diuretic. Patients should have a daytime mean systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM at least 4 weeks after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period and DB Extension period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months

ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 44 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 18 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

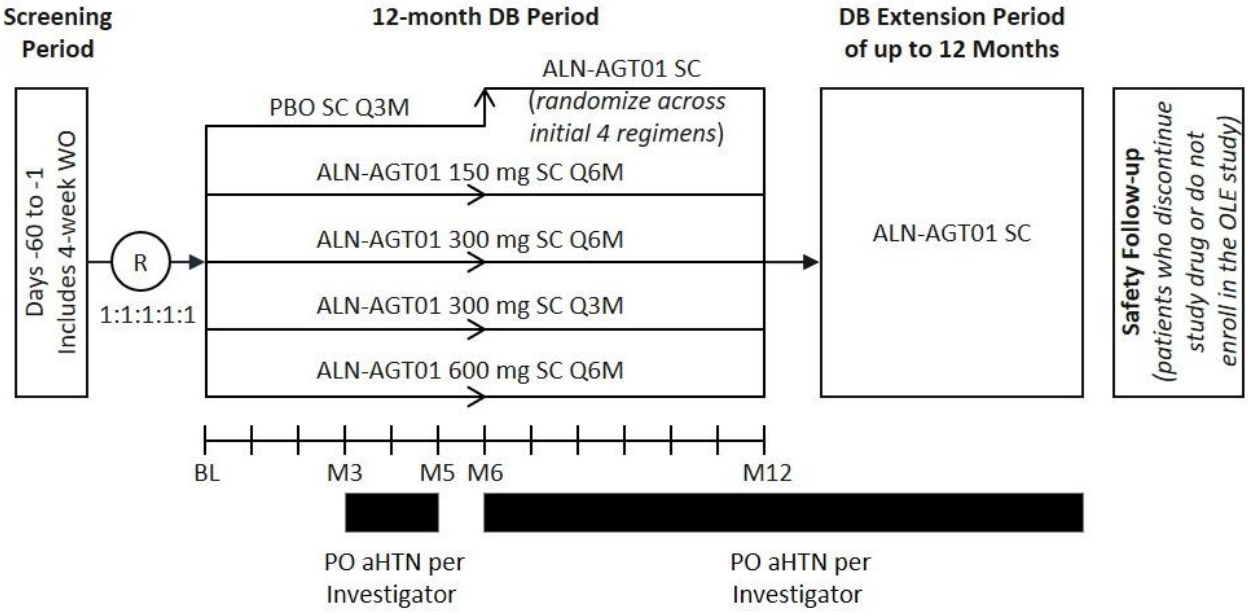
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 evaluable postdose blood sample for the determination of plasma ALN-AGT01 concentrations.
- **PD Analysis Set**: All patients who received any amount of study drug and who have baseline and at least 1 postdose blood sample for the determination of serum AGT will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.
Note: Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Sections 6.2	X			X		X			X		X		X	X	X	X	X
HBPM[c,f]	Section 6.2	X	At least 3 times/week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
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Neurological evaluation and symptom-directed physical exam	Section 6.5.3						X			X				X		X		X
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
24-hour urine for aldosterone, sodium, and creatinine	Sections 6.5.5 and 6.6	X					X			X					X			
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X				X	X	X	X	X

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
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Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)	Section 6.5.5.2		X				X			X				X	X	X	X	X
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: renin and aldosterone	Section 6.3		X	X	X	X	X			X					X	X	X	
RAAS biomarkers: AngI/II	Section 6.3		X				X			X					X			
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	X
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									
Study drug administration	Section 5.2.2		X				X			X				X	X	X		

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
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Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous																
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections should be performed before physical examinations and 12-lead ECGs.
- Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may receive a dose of ALN-AGT01 at the Month 12 visit and continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first). Patients who rollover at Month 12 should complete all assessments scheduled for the Month 12 visit except for study drug administration. Patients who rollover at Months 18 or 24 should complete the EOT visit instead of the assessments scheduled at those visits.
- Patients who do not enroll in the OLE study will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14

- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 4 weeks of washout.

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.

[e] ABPM recordings associated with dosing visits should be obtained within 7 days before the dosing visit and results reviewed before dosing. ABPM should only be collected at Months 18 and 24 for patients in the DB Extension period.

[f] HBPM must be measured in the morning upon waking. HBPM should be measured daily between Months 5 and 6 if oral antihypertensives are temporarily held. HBPM is not required at times when ABPM is being assessed.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour:minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Definition
ISR	Injection site reaction
LFT	Liver function test
MAO	Monoamine oxidase
MCP-Mod	Multiple comparison-modeling
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01, a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock and Krousel-Wood 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension

and to overcome the limitations of current therapies is a key unmet need.[Dzau and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease

population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM and response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 4 weeks.

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, home blood pressure monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM). Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the ALN-AGT01 OLE study will be asked to complete Safety Follow-up visits after their last dose of study drug:

- Patients who discontinue study drug before Month 6: Safety Follow-up visits will occur once every 6 months after the last dose of study drug until the last patient's Month 6 visit or until serum AGT levels return to ≥50% of their individual mean baseline level, whichever comes later.
- Patients who discontinue study drug after the Month 6 visit: Safety Follow-up visits will occur once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level.

Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 44 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 18 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for at least 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe systolic hypertension (SBP ≥180 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a calcium channel blocker (CCB) and/or thiazide/thiazide-like diuretic will be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by daily HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer for treatment of potential hyperkalemia.[Georgianos and

Agarwal 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months

- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. After the database lock to support the analysis of Month 6 data is complete, the Sponsor will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after the analysis of Month 12 data is complete.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 12 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the OLE study.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with 1 or more antihypertensive medications of the following classes: an ACE inhibitor, ARB, renin inhibitor, CCB, thiazide diuretic, and/or thiazide-like diuretic. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Daytime mean SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥4 weeks prior to this ABPM.

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension
2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 4 weeks of washout:
   a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
   b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
   c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
   d. Elevated potassium >5 mEq/L
   e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the course of the study any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking, or taken within 30 days prior to randomization, beta blockers
7. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the course of the study sodium-glucose co-transporter 2 (SGLT2) inhibitors
8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. In addition, chronic/standing use of over-the-counter NSAIDs is not permitted. Paracetamol/acetaminophen (up to 2 g per day) for analgesia will be allowed.

9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the course of the study
10. Received an RNAi therapeutic (approved or investigational) within 6 months prior to randomization

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.0%), newly diagnosed Type 2 diabetes mellitus (within 6 months prior to randomization), or laboratory evidence of diabetes during screening (fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], random plasma glucose ≥200 mg/dL [11.1 mmol/L], or HbA1c ≥6.5%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening
16. Has known human immunodeficiency virus or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization
25. Known change in body weight >10% in last 6 months prior to screening

26. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
27. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
29. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
31. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
32. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

33. Third shift or night shift workers
34. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
35. Unable or unwilling to perform HBPM as specified

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion
- AE

- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (excluding PK assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until the last patient's Month 6 visit or until PD recovery (whichever is later); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete end of treatment (EOT)/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery; see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be

informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period. Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. If an alternative cause is found, provide appropriate care.
   c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

Transaminase Level	Action
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored upright and refrigerated at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.7. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.8. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the investigational product and its packaging after it is released for distribution at clinical site.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that investigational product complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, contamination of investigational product, and malfunction of syringe needle safety device.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6 instructions on reporting CPCs will also be detailed in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure will be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should be evaluated at the clinical study site or another hospital setting within 24 hours. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure.
- The Investigator should consider downtitration or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <100 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <110 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.
- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated or discontinued.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.
- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe systolic hypertension (office SBP ≥180 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. • If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	Intervene if clinically significant blood pressure elevation: • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.
Months 3 to 6	Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic: • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic should be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent

Study Period	Intervention
	– Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)
Month 6 to End of Study	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, prior oral antihypertensive should be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM. • Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- Study drug (and additional oral antihypertensive agents, if applicable) should be prophylactically held during intercurrent illness or volume depletion
- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction
- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should look for potentially reversible causes of renal dysfunction and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ ≥5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia.[a] Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains ≥5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards) • Consider interruption of ALN-AGT01, according to Investigator medical judgment.	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of ALN-AGT01, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer	• Immediately interrupt ALN-AGT01 • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer • Apply all measures outlined for serum K^+ ≥5.5 and < 6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer will be assessed at participating study sites. This potassium-binding drug is approved for the treatment of hyperkalemia and has been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant

medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Occasional use of systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, Investigators will titrate therapy with oral antihypertensives to a target blood pressure range (office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg). All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin)
- Prescription NSAIDs
- Chronic/standing use of nonprescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride).

- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently

sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to

dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs and weight (at the discretion of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed by the patient or legal guardian before the screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 4 weeks of washout and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once as described in Section 6.2.1, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 4 weeks must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. HBPM must be collected after at least 4 weeks of

washout for at least 2 consecutive weeks (at least 3 recordings per week) prior to randomization to establish baseline.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM must be started prior to the morning dose of antihypertensive medication.

Adequacy will be assessed for all ABPMs. If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

See further details in Section 10.1 and the Study Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Approximately 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained

after at least 4 weeks of washout. Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Study Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples collected for AngI and AngII require special processing and will be assessed at sites that have appropriate resources, equipment, and reagents. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Levels of aldosterone will also be analyzed in urine collections at the time points listed in the Schedule of Assessments (Table 1). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide other elements of study conduct or clinical management and will not be shared with sites until after study completion. If clinical circumstances arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and

recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status (see the Study Manual for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed

according to the Study Manual during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection occur at the same visit, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning. A 24-hour urine collection for aldosterone, sodium, and creatinine will be performed at time points listed in

the Schedule of Assessments (Table 1). These 24-hour collections should be obtained within 2 days before the ABPM associated with the same visit.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Hepatitis Tests	
Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBsAg, HBc antibody IgM and IgG

Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HbA1c=hemoglobin A1c; HBc=hepatitis B virus core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HDL-C=high-density lipoprotein; HEV=hepatitis E virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LDL-C=low-density lipoprotein; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy

testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen

Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or

hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. ‘Severity’ characterizes the intensity of an AE. ‘Serious’ is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the study drug?” A “yes” response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient’s health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications,

or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event

- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious adverse events must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). In addition to the dedicated collections for optional exploratory biomarkers (urine, plasma, serum), aliquots from each 24-hour urine collection will be archived for potential exploratory investigations. These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05. Table 8 shows the statistical power with various standard deviation assumptions.

Table 8: Statistical Power to Detect 10 mmHg Difference Between ALN-AGT01 and Placebo With Various Standard Deviation Assumptions

Assumption of Standard Deviation (mmHg)	Statistical Power to Detect Dose Response Trend (%)	Statistical Power to Detect Difference Between an Individual ALN-AGT01 Dose Versus Placebo (%)
15	97	96
18	90	88
20	84	80

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 evaluable postdose blood sample for the determination of plasma ALN-AGT01 concentrations.
- **PD Analysis Set**: All patients who received any amount of study drug and who have baseline and at least 1 postdose blood sample for the determination of serum AGT will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change in SBP from baseline at Month 3 assessed by ABPM. The primary hypothesis of the dose response relationship for the primary endpoint across ALN-AGT01 doses and placebo will be tested using a multiple comparison– modeling (MCP Mod) approach.[Bretz 2005] The presence of a dose-response trend will be initially tested against a set of prespecified dose-response models at a 2-sided significance level of 0.05, adjusted for multiplicity (the MCP step). Several candidate models will be prespecified in the SAP. Then, the dose-response curves will be further estimated (the modeling step) based on the ‘best’ fitted dose response model. Furthermore, each ALN-AGT01 dose group will be compared against placebo using Dunnett’s Test.

For the secondary endpoints of change in DBP assessed by ABPM at Month 3 and change in SBP and DBP assessed by ABPM at Month 6, each ALN-AGT01 dose group will be compared with placebo. For change in office SBP and DBP, each ALN-AGT01 dose group will be compared with placebo at Month 3 and Month 6 and also using the time-adjusted average from Month 1 to Month 3 and from Month 1 to Month 6.

No multiplicity adjustment is applied across primary and secondary endpoints.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

The primary analysis will be conducted after all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit. No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be

destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must

also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the Study Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with adequacy assessment. An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 2 days. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel who will bring an office blood pressure instrument to the

patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM every morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient must measure HBPM for at least 2 consecutive weeks (and with at least 3 successful readings per week) prior to randomization. Patients previously taking medication for hypertension must be without antihypertensives for ≥4 weeks prior to collecting these baseline HBPM measurements. If adequate baseline HBPM data (at least 3 successful readings per week for at least 2 consecutive weeks) are not collected within the Screening period, the patient is a screen failure.

After Day 1, HBPM should be measured at least 3 times per week. Patients may select the 3 days of the week that are most convenient for their personal schedule. The frequency of HBPM monitoring should be increased to daily during the temporary hold of oral antihypertensives performed in some patients from Month 5 to Month 6.

CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 20 APRIL 2021

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021 Amendment 1, 20 April 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted] MD [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

[redacted] MD

[redacted]

Alnylam Pharmaceuticals, Inc.

21 april 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 50 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM and response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic

of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 4 weeks. Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by daily home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with 1 or more antihypertensive medications of the following classes: an angiotensin converting enzyme inhibitor, angiotensin II-receptor blocker, renin inhibitor, calcium channel blocker, thiazide diuretic, and/or thiazide-like diuretic. Patients should have a daytime mean systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM at least 4 weeks after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period and DB Extension period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months

ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 44 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 18 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

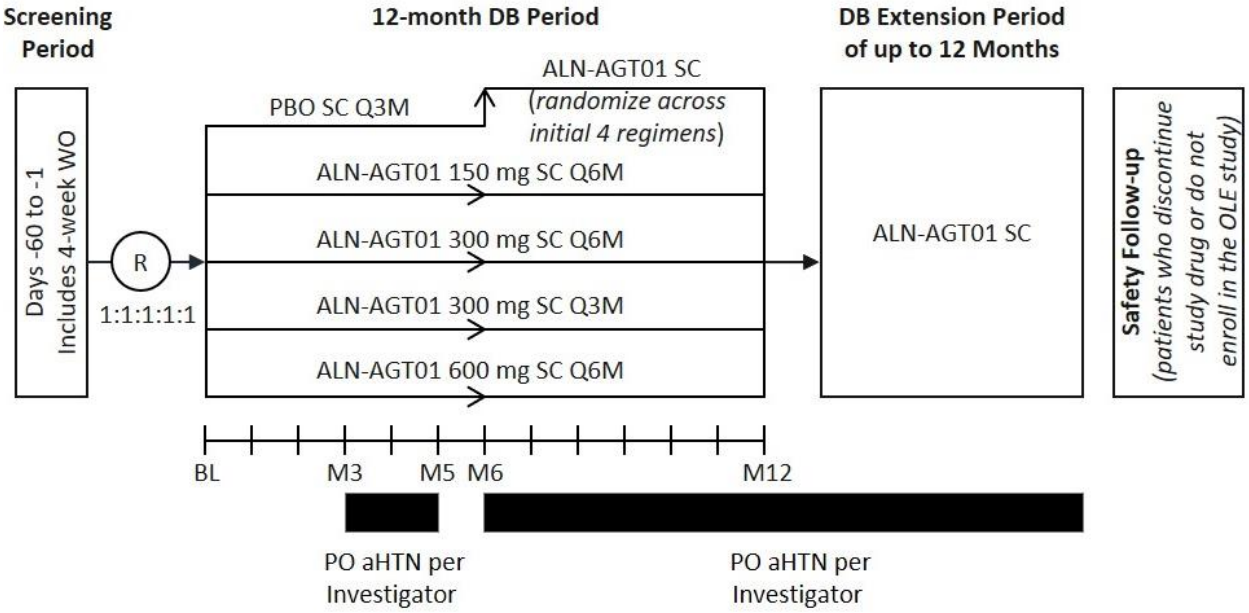
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 evaluable postdose blood sample for the determination of plasma ALN-AGT01 concentrations.
- **PD Analysis Set**: All patients who received any amount of study drug and who have baseline and at least 1 postdose blood sample for the determination of serum AGT will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.
Note: Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Sections 6.2	X			X		X			X		X		X	X	X	X	X
HBPM[c,f]	Section 6.2	X	At least 3 times/week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	
Symptom-directed physical exam	Section 6.5.3						X			X				X		X		X

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
24-hour urine for aldosterone, sodium, and creatinine	Sections 6.5.5 and 6.6	X					X			X					X			
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X				X	X	X	X	X
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)	Section 6.5.5.2		X				X			X				X	X	X	X	X

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: renin and aldosterone	Section 6.3		X	X	X	X	X			X					X	X	X	
RAAS biomarkers: AngI/II	Section 6.3		X				X			X					X			
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	X
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									
Study drug administration	Section 5.2.2		X				X			X				X	X	X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous																
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone;

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14

HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections should be performed before physical examinations and 12-lead ECGs.
- Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may receive a dose of ALN-AGT01 at the Month 12 visit and continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first). Patients who rollover at Month 12 should complete all assessments scheduled for the Month 12 visit except for study drug administration. Patients who rollover at Months 18 or 24 should complete the EOT visit instead of the assessments scheduled at those visits.
- Patients who do not enroll in the OLE study will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 4 weeks of washout.

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.

[e] ABPM recordings associated with dosing visits should be obtained within 7 days before the dosing visit and results reviewed before dosing. ABPM should only be collected at Months 18 and 24 for patients in the DB Extension period.

[f] HBPM must be measured in the morning upon waking. HBPM should be measured daily between Months 5 and 6 if oral antihypertensives are temporarily held. HBPM is not required at times when ABPM is being assessed.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour:minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Definition
ISR	Injection site reaction
LFT	Liver function test
MAO	Monoamine oxidase
MCP-Mod	Multiple comparison-modeling
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01, a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock and Krousel-Wood 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension

and to overcome the limitations of current therapies is a key unmet need.[Dzau and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease

population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM and response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 4 weeks.

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, home blood pressure monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM). Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the ALN-AGT01 OLE study will be asked to complete Safety Follow-up visits after their last dose of study drug:

- Patients who discontinue study drug before Month 6: Safety Follow-up visits will occur once every 6 months after the last dose of study drug until the last patient's Month 6 visit or until serum AGT levels return to ≥50% of their individual mean baseline level, whichever comes later.
- Patients who discontinue study drug after the Month 6 visit: Safety Follow-up visits will occur once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level.

Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 44 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 18 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for at least 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe systolic hypertension (SBP ≥180 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a calcium channel blocker (CCB) and/or thiazide/thiazide-like diuretic will be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by daily HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer for treatment of potential hyperkalemia.[Georgianos and

Agarwal 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months

- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24-hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. After the database lock to support the analysis of Month 6 data is complete, the Sponsor will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after the analysis of Month 12 data is complete.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 12 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the OLE study.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with 1 or more antihypertensive medications of the following classes: an ACE inhibitor, ARB, renin inhibitor, CCB, thiazide diuretic, and/or thiazide-like diuretic. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Daytime mean SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥4 weeks prior to this ABPM.

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension
2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 4 weeks of washout:
   a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
   b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
   c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
   d. Elevated potassium >5 mEq/L
   e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the course of the study any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking, or taken within 30 days prior to randomization, beta blockers
7. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the course of the study sodium-glucose co-transporter 2 (SGLT2) inhibitors
8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. In addition, chronic/standing use of over-the-counter NSAIDs is not permitted. Paracetamol/acetaminophen (up to 2 g per day) for analgesia will be allowed.

9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the course of the study
10. Received an RNAi therapeutic (approved or investigational) within 6 months prior to randomization

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.0%), newly diagnosed Type 2 diabetes mellitus (within 6 months prior to randomization), or laboratory evidence of diabetes during screening (fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], random plasma glucose ≥200 mg/dL [11.1 mmol/L], or HbA1c ≥6.5%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening
16. Has known human immunodeficiency virus or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization
25. Known change in body weight >10% in last 6 months prior to screening

26. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
27. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
29. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
31. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
32. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

33. Third shift or night shift workers
34. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
35. Unable or unwilling to perform HBPM as specified

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion
- AE

- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (excluding PK assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until the last patient's Month 6 visit or until PD recovery (whichever is later); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete end of treatment (EOT)/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery; see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be

informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period. Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. If an alternative cause is found, provide appropriate care.
   c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

Transaminase Level	Action
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored upright and refrigerated at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.6. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.7. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the investigational product and its packaging after it is released for distribution at clinical site.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that investigational product complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, contamination of investigational product, and malfunction of syringe needle safety device.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6 instructions on reporting CPCs will also be detailed in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure will be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should be evaluated at the clinical study site or another hospital setting within 24 hours. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure.
- The Investigator should consider downtitration or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <100 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <110 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the

Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.

- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated or discontinued.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.
- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe systolic hypertension (office SBP ≥180 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study.

Study Period	Intervention
	• If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic:</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic should be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent – Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)
Month 6 to End of Study	<u>Treat to target blood pressure using Investigator's choice of oral antihypertensive(s)</u>. • At Month 6, prior oral antihypertensive should be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM.

Study Period	Intervention
	• Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- Study drug (and additional oral antihypertensive agents, if applicable) should be prophylactically held during intercurrent illness or volume depletion
- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction
- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should look for potentially reversible causes of renal dysfunction and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ ≥5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia.[a] Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains ≥5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards) • Consider interruption of ALN-AGT01, according to Investigator medical judgment.	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of ALN-AGT01, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer	• Immediately interrupt ALN-AGT01 • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer • Apply all measures outlined for serum K^+ ≥5.5 and < 6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer will be assessed at participating study sites. This potassium-binding drug is approved for the treatment of hyperkalemia and has been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant

medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Occasional use of systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, Investigators will titrate therapy with oral antihypertensives to a target blood pressure range (office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg). All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin)
- Prescription NSAIDs
- Chronic/standing use of nonprescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride).

- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently

sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to

dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs and weight (at the discretion of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed by the patient or legal guardian before the screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 4 weeks of washout and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once as described in Section 6.2.1, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 4 weeks must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. HBPM must be collected after at least 4 weeks of

washout for at least 2 consecutive weeks (at least 3 recordings per week) prior to randomization to establish baseline.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM must be started prior to the morning dose of antihypertensive medication.

Adequacy will be assessed for all ABPMs. If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

See further details in Section 10.1 and the Study Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Approximately 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained

after at least 4 weeks of washout. Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Study Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples collected for AngI and AngII require special processing and will be assessed at sites that have appropriate resources, equipment, and reagents. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Levels of aldosterone will also be analyzed in urine collections at the time points listed in the Schedule of Assessments (Table 1). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide other elements of study conduct or clinical management and will not be shared with sites until after study completion. If clinical circumstances arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and

recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection occur at the same visit, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning. A 24-hour urine collection for aldosterone, sodium, and creatinine will be performed at time points listed in the Schedule of Assessments (Table 1). These 24-hour collections should be obtained within 2 days before the ABPM associated with the same visit.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Hepatitis Tests	
Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBsAg, HBc antibody IgM and IgG
Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin

Fasting glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HbA1c=hemoglobin A1c; HBc=hepatitis B virus core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HDL-C=high-density lipoprotein; HEV=hepatitis E virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LDL-C=low-density lipoprotein; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen

Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious adverse events must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). In addition to the dedicated collections for optional exploratory biomarkers (urine, plasma, serum), aliquots from each 24-hour urine collection will be archived for potential exploratory investigations. These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05. Table 8 shows the statistical power with various standard deviation assumptions.

Table 8: Statistical Power to Detect 10 mmHg Difference Between ALN-AGT01 and Placebo With Various Standard Deviation Assumptions

Assumption of Standard Deviation (mmHg)	Statistical Power to Detect Dose Response Trend (%)	Statistical Power to Detect Difference Between an Individual ALN-AGT01 Dose Versus Placebo (%)
15	97	96
18	90	88
20	84	80

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.

- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 evaluable postdose blood sample for the determination of plasma ALN-AGT01 concentrations.
- **PD Analysis Set**: All patients who received any amount of study drug and who have baseline and at least 1 postdose blood sample for the determination of serum AGT will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change in SBP from baseline at Month 3 assessed by ABPM. The primary hypothesis of the dose response relationship for the primary endpoint across ALN-AGT01 doses and placebo will be tested using a multiple comparison– modeling (MCP Mod) approach.[Bretz 2005] The presence of a dose-response trend will be initially tested against a set of prespecified dose-response models at a 2-sided significance level of 0.05, adjusted for multiplicity (the MCP step). Several candidate models will be prespecified in the SAP. Then, the dose-response curves will be further estimated (the modeling step) based on the 'best' fitted dose response model. Furthermore, each ALN-AGT01 dose group will be compared against placebo using Dunnett's Test.

For the secondary endpoints of change in DBP assessed by ABPM at Month 3 and change in SBP and DBP assessed by ABPM at Month 6, each ALN-AGT01 dose group will be compared with placebo. For change in office SBP and DBP, each ALN-AGT01 dose group will be

compared with placebo at Month 3 and Month 6 and also using the time-adjusted average from Month 1 to Month 3 and from Month 1 to Month 6.

No multiplicity adjustment is applied across primary and secondary endpoints.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for

laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

The primary analysis will be conducted after all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit. No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be

destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must

also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the Study Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with adequacy assessment. An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 2 days. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel who will bring an office blood pressure instrument to the

patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM every morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient must measure HBPM for at least 2 consecutive weeks (and with at least 3 successful readings per week) prior to randomization. Patients previously taking medication for hypertension must be without antihypertensives for ≥4 weeks prior to collecting these baseline HBPM measurements. If adequate baseline HBPM data (at least 3 successful readings per week for at least 2 consecutive weeks) are not collected within the Screening period, the patient is a screen failure.

After Day 1, HBPM should be measured at least 3 times per week. Patients may select the 3 days of the week that are most convenient for their personal schedule. The frequency of HBPM monitoring should be increased to daily during the temporary hold of oral antihypertensives performed in some patients from Month 5 to Month 6.

CLINICAL STUDY PROTOCOL
ALN-AGT01-002
DATED 09 APRIL 2021

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension
Short Title:	A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)
Study Drug:	ALN-AGT01
EudraCT Number:	2021-001248-82
IND Number:	143503
Protocol Date:	Original protocol, 09 April 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted] MD [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]
[redacted] MD
[redacted]

Alnylam Pharmaceuticals, Inc.

9 April 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension

Short Title

A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients with Mild-to-Moderate Hypertension (KARDIA-1)

Study Drug

ALN-AGT01

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 50 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM and response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered subcutaneously (SC), in patients with mild-to-moderate hypertension. A schematic

of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 4 weeks. Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will receive ALN-AGT01 or placebo for the first 6 months of the 12-month Double-blind (DB) treatment period.

Starting at Month 3, conventional oral antihypertensives may be added per Investigator judgement for elevated blood pressure. Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ambulatory blood pressure monitoring (ABPM). During this 4-week period, blood pressure will be carefully monitored by daily home blood pressure monitoring and medications restarted if indicated. Patients may resume conventional oral antihypertensives at Month 6 per Investigator judgement.

Patients randomized to placebo will be re-randomized at Month 6 to 1 of the 4 initial ALN-AGT01 regimens until the end of the DB period. Patients randomized to ALN-AGT01 regimens will remain on their originally assigned regimens through Month 12.

After the 12-month DB treatment period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

Number of Planned Patients

Approximately 375 patients will be enrolled in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with 1 or more antihypertensive medications of the following classes: an angiotensin converting enzyme inhibitor, angiotensin II-receptor blocker, renin inhibitor, calcium channel blocker, thiazide diuretic, and/or thiazide-like diuretic. Patients should have a mean 24-hour systolic blood pressure (SBP) ≥135 mmHg and ≤160 mmHg by ABPM at least 4 weeks after washout of background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

ALN-AGT01 is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive ALN-AGT01 will be administered 150 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 6 months, 300 mg ALN-AGT01 SC once every 3 months, or 600 mg ALN-AGT01 SC once every 6 months during the 12-month DB period and DB Extension period. Patients randomized to receive placebo will be randomized to 1 of the 4 initial dose regimens of ALN-AGT01 beginning at Month 6.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered once every 3 months and at the same volume as the study drug. Patients receiving once every 6 months

ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Duration of Treatment and Study Participation

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 44 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 18 months in the Follow-up period.

Statistical Methods

The planned enrollment for this study is 375 patients. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24 hour SBP < or ≥145 mmHg).

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05.

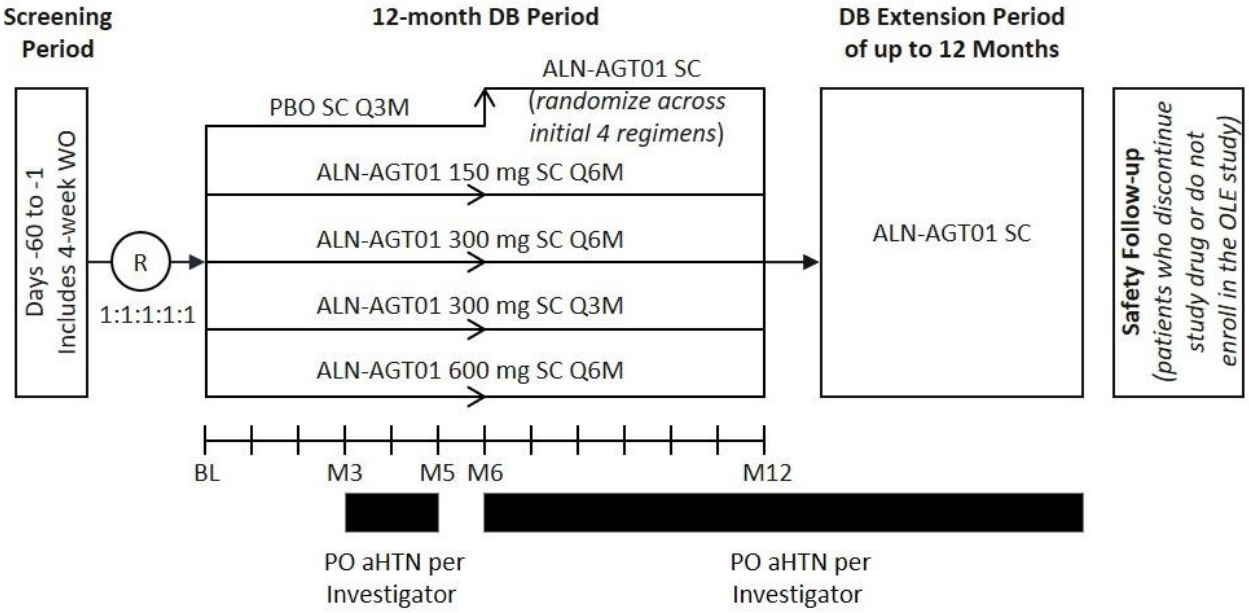
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 evaluable postdose blood sample for the determination of plasma ALN-AGT01 concentrations.
- **PD Analysis Set**: All patients who received any amount of study drug and who have baseline and at least 1 postdose blood sample for the determination of serum AGT will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medications; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); Q3M=once every 3 months; Q6M=once every 6 months; R=randomization; SC=subcutaneous; WO=washout.
Note: Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Informed consent	Section 8.1.1	X																
Medical history	Section 6.1	X																
Demographics		X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X																
Oral antihypertensive medication washout of at least 4 weeks	Section 3.1	X																
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3 To confirm post-menopausal status if applicable	X																
Vital signs and office blood pressure[c,d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c,e]	Sections 6.2	X			X		X			X		X		X	X	X	X	X
HBPM[c,f]	Section 6.2	X	At least 3 times/week															
Optional exploratory wearable blood pressure measurements	Section 6.2.4	X					X											
Full physical exam	Section 6.5.3	X	X												X		X	
Symptom-directed physical exam	Section 6.5.3						X			X				X		X		X

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Height, body weight, and BMI	Section 6.5.2; Height measured at screening only	X	X				X			X					X	X	X	X
Single 12-Lead ECG	Section 6.5.4	X	X												X		X	
Serum chemistry[c]	Table 6; Section 6.5.5	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X	X				X			X				X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.2.4	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
24-hour urine for aldosterone, sodium, and creatinine	Sections 6.5.5 and 6.6	X					X			X					X			
Spot urine for albumin and creatinine	Section 6.5.5	X	X				X			X				X	X	X	X	
Fasting glucose, insulin, lipid panel, and HbA1c	Section 6.5.5.1	X	X				X			X				X	X	X	X	X
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior		X							X								
Plasma for PK	Section 6.4 and Table 2		X							X								
Immunogenicity (ADA)	Section 6.5.5.2		X				X			X				X	X	X	X	X

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]													DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14
Serum AGT	Section 6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAAS biomarkers: renin and aldosterone	Section 6.3		X	X	X	X	X			X					X	X	X	
RAAS biomarkers: AngI/II	Section 6.3		X				X			X					X			
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X			X				X	X	X	X	
Waist circumference and waist-to-hip ratio	Section 6.5.2		X				X			X					X		X	X
Exploratory DNA sample (optional)	Section 6.6		X															
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7		X				X			X				X	X	X	X	
Temporary hold of oral antihypertensives	Section 3.1 and Table 4								X									
Study drug administration	Section 5.2.2		X				X			X				X	X	X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous																
Concomitant medications	Section 5.5	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone;

Shading indicates visits that must be performed at the site		Screening Period	Double-blind Period[a]												DB Extension Period[a]	EOT/ET	Safety Follow-up
Study Visit (Month)				W2	M1	M2	M3	M4	M5	M6	M6.5	M7	M8	M9	M12			Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1	D1	D15±2	D29 ±2	D57 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D183 ±7	D197 ±7	D225 ±7	D253 ±7	D337±7	Q3M ±14	M24±14	±14

HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q3M=once every 3 months; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections should be performed before physical examinations and 12-lead ECGs.
- Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may receive a dose of ALN-AGT01 at the Month 12 visit and continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first). Patients who rollover at Month 12 should complete all assessments scheduled for the Month 12 visit except for study drug administration. Patients who rollover at Months 18 or 24 should complete the EOT visit instead of the assessments scheduled at those visits.
- Patients who do not enroll in the OLE study will be asked to perform Safety Follow-up visits q6M after the last dose of study drug as described in Section 3.1. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed. See Section 4.3.1 for instructions for patients who discontinue study drug.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to dosing at dosing visits.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after at least 4 weeks of washout.

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications.

[e] ABPM recordings associated with dosing visits should be obtained within 7 days before the dosing visit and results reviewed before dosing. ABPM should only be collected at Months 18 and 24 for patients in the DB Extension period.

[f] HBPM must be measured in the morning upon waking. HBPM should be measured daily between Months 5 and 6 if oral antihypertensives are temporarily held. HBPM is not required at times when ABPM is being assessed.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±1 h)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±1 h)	X

Abbreviations: hh:mm=hour:minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody(ies)
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Definition
ISR	Injection site reaction
LFT	Liver function test
MAO	Monoamine oxidase
MCP-Mod	Multiple comparison-modeling
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
q3M	Once every 3 months
q6M	Once every 6 months
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing ALN-AGT01, a subcutaneously (SC) administered investigational agent comprised of a synthetic small interfering (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-002 (KARDIA-1) is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and pharmacodynamics (PD) of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. Patients will be randomized to 1 of 4 ALN-AGT01 treatment regimens or placebo for the first 6 months of the 12-month Double-blind (DB) period. After the first 6 months of the DB period, patients from the placebo arm will be re-randomized to 1 of the 4 initial ALN-AGT01 regimens for the remaining 6 months of the DB period, while patients randomized to ALN-AGT01 will remain on their originally assigned regimens. After completion of the 12-month DB period, patients may be eligible to participate in an ALN-AGT01 open-label extension (OLE) study. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of ALN-AGT01 for the treatment of hypertension by evaluating the impact on systolic blood pressure (SBP) from baseline to Month 3, as assessed by ambulatory blood pressure monitoring (ABPM). Secondary and exploratory objectives of the study include evaluating the efficacy of ALN-AGT01 on other measures of blood pressure response and evaluating the PD effect of ALN-AGT01, including reduction in circulating AGT concentration.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock and Krousel-Wood 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension

and to overcome the limitations of current therapies is a key unmet need.[Dzau and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing ALN-AGT01, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent suppression of the synthesis and levels of the target protein. ALN-AGT01 contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, ALN-AGT01 is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin-aldosterone system (RAAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, ALN-AGT01 has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II (AngII).

Preliminary data from Part A of the ongoing Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension have shown that single SC doses of ALN-AGT01 lead to dose-dependent and durable reductions in circulating AGT, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Reductions in AGT for up to 6 months postdose were observed in the study.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium, and no patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in Part A patients who received ALN-AGT01 doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

This Phase 2 study will further quantify the antihypertensive effects of ALN-AGT01 across a range of doses (150 to 600 mg) and dose intervals (once every 3 months and once every 6 months) to identify optimal treatment. The consistent and prolonged PD effect of ALN-AGT01 is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALN-AGT01 is provided in the Investigator's Brochure.

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that ALN-AGT01 may offer the benefit of blood pressure reduction to patients with hypertension. The mean SBP reduction observed after single ALN-AGT01 doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives. The blood pressure of patients will be closely monitored, and after Month 3, oral antihypertensives will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of ALN-AGT01, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with ALN-AGT01. Based upon the disease

population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, and add-on treatments are permitted to avoid prolonged periods of untreated hypertension. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.4.1), hypertension (Section 5.4.2), renal dysfunction (Section 5.4.3), and hyperkalemia (Section 5.4.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from Study 001, ALN-AGT01 has an acceptable safety profile. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

Information about the known and expected benefits and risks of ALN-AGT01 may also be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ALN-AGT01 on SBP as assessed by ABPM at Month 3	• Change in SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the effect of ALN-AGT01 on blood pressure assessed by ABPM • To evaluate the effect of ALN-AGT01 on office blood pressure • To characterize the PD effects of ALN-AGT01	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Change in serum AGT
Exploratory	
• To evaluate the effect of ALN-AGT01, over time, on other measures of blood pressure reduction (through Month 12)	• Change in SBP and DBP assessed by ABPM • Change in office SBP and DBP • Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM and response rate (by blood pressure normalization)

Objectives	Endpoints
	• Proportion of patients with oral antihypertensive use • Change in SBP and DBP assessed by HBPM • Change in daytime and nighttime blood pressure (including dipping pattern)
• To characterize the PD effects of ALN-AGT01 (after Month 6)	• Change in serum AGT
• To characterize the plasma PK of ALN-AGT01	• Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01
• To assess the effect of ALN-AGT01 on exploratory biomarkers of the RAAS	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of ALN-AGT01	• Incidence and titers of ADA
• To assess the effect of ALN-AGT01 on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of ALN-AGT01 on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, and serum lipid profile
• To correlate blood pressure measurements obtained with a wearable, noninvasive, cuffless device to those obtained by standard cuff-based methods	• Correlation of blood pressure values obtained with a wearable device versus ABPM, HBPM, and office measurements
• To assess the long-term treatment effect of ALN-AGT01 (through Month 24)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of ALN-AGT01 in patients with mild to moderate hypertension	• Frequency of AEs

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. A schematic of the study design is provided in Figure 1. Before randomization, patients will discontinue prior antihypertensive medications (if taking) for a Washout period of at least 4 weeks.

DB and DB Extension Periods

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized 1:1:1:1:1 to receive 1 of the following regimens over a 12-month DB treatment period. Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24 hour SBP < or ≥145 mmHg).

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for daytime mean SBP ≥135 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, home blood pressure monitoring [HBPM] SBP <135 mmHg, or daytime mean SBP <135 mmHg by ABPM). Oral antihypertensives (if taking) will be temporarily held from Month 5 to Month 6 in appropriate patients (Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent or office SBP <150 mmHg if taking 2 agents) to assess the effect of ALN-AGT01 alone (vs placebo) at Month 6 by ABPM. During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms).

Patients may be eligible to participate in an ALN-AGT01 OLE study upon completion of the Month 12 predose assessments. If an individual patient reaches Month 12 prior to availability of the OLE study, they may continue their current blinded dosing in the DB Extension period for up to 12 additional months until the OLE study is open and then transition. Once the OLE study is open for enrollment, eligible patients may rollover into the OLE study at Months 12, 18, or 24 (whichever visit occurs first).

In the DB Extension period, blood pressure will be closely monitored and individual modification of antihypertensive therapy will be allowed to maintain blood pressure in target range.

Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the ALN-AGT01 OLE study will be asked to complete Safety Follow-up visits after their last dose of study drug:

- Patients who discontinue study drug before Month 6: Safety Follow-up visits will occur once every 6 months after the last dose of study drug until the last patient's Month 6 visit or until serum AGT levels return to ≥50% of their individual mean baseline level, whichever comes later.
- Patients who discontinue study drug after the Month 6 visit: Safety Follow-up visits will occur once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level.

Patients who discontinue study drug prior to the Month 6 visit will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, early termination (ET) assessments should be performed.

The planned enrollment for this study is approximately 375 patients (75 patients per group).

The duration of treatment with ALN-AGT01 is up to 24 months. The estimated total time on study for each patient is up to 44 months, including up to 2 months of screening, followed by up to 24 months of treatment, and up to 18 months in the Follow-up period.

3.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, multicenter Phase 2 study designed to evaluate the safety, efficacy, and PD of ALN-AGT01, administered SC, in patients with mild-to-moderate hypertension. The primary objective of the study is to evaluate the efficacy of ALN-AGT01 by measuring the impact on SBP from baseline to Month 3, as assessed by ABPM.

This study will quantify the antihypertensive effects of ALN-AGT01 across a range of doses and dose intervals to identify optimal treatment regimens for study in Phase 3.

Patients will discontinue prior antihypertensive medications (if taking) for at least 4 weeks prior to study drug administration. During the study, blood pressure will be monitored with both outpatient 24-hour ABPM and automated office blood pressure measurements (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). The primary endpoint will be assessed by ABPM given its greater precision over office blood pressure measurements. In addition, 24-hour ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 21% to 35% of hypertensive patients).[de la Sierra 2009; White 1998] More frequent measurements will be collected through a third method, oscillometric HBPM, to assess long-term blood pressure variability and provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), the first 6 months of the DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, individual modification of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting at Month 3 and will continue throughout the study (except between Month 5 and Month 6 as described in Section 3.1). Separate from these treat-to-target modifications, any confirmed event of severe systolic hypertension (SBP ≥180 mmHg) will be appropriately treated regardless of its timing relative to study drug administration.

If a patient requires treatment with a conventional oral antihypertensive before Month 6, a calcium channel blocker (CCB) and/or thiazide/thiazide-like diuretic will be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS. Additionally, their blood pressure effects are expected to washout within 4 weeks.

Rigorous assessment of the antihypertensive effects of ALN-AGT01 at Month 6 (trough for the once every 6 month regimens) relative to placebo is critical to evaluate the feasibility of once every 6 month dosing regimens for future study in Phase 3. Accordingly, oral antihypertensives (if taking) will be temporarily held from Month 5 to the Month 6 ABPM assessment. For each patient, this limited interruption in oral antihypertensives will be contingent upon the patient's Month 5 office SBP being adequately controlled (see Table 4) and the Investigator's assessment that interruption can be safely performed and carefully monitored by daily HBPM measurements. Of note, a withdrawal period is a standard element in studies of oral antihypertensives that is often used to establish assay sensitivity, to demonstrate maintenance of efficacy, and to assess possible withdrawal effects (ICH E12A; Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000). Outside of research studies, antihypertensives are temporarily discontinued in clinical practice for diagnostic purposes, and interruptions up to 6 weeks have been shown to be safe.[Beeftink 2017] In this study, the period of interruption is limited to 4 weeks, and most patients are expected to have continued antihypertensive effect from ALN-AGT01. If a clinically significant blood pressure elevation (confirmed SBP >170 mmHg; or SBP >160 mmHg accompanied by symptoms) occurs after the interruption of oral antihypertensives, Investigators will instruct the patient to promptly resume dosing with their existing supply of oral medication.

After Month 6, other oral antihypertensives may be used at the discretion of the Investigator, following current care guidelines.[Whelton 2018; Williams 2018] Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study. Blood pressure and pharmacokinetic (PK)/PD assessments will be collected through Month 12 to assess the effect of repeated dosing.

While tissue specificity of ALN-AGT01 for the liver is hypothesized to improve tolerability relative to current oral antihypertensives,[Mullick 2017; Uijl 2019] the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS inhibitors,[McMurray 2016; Parving 2012] with improvements to include the use of the newer oral potassium binder patiromer for treatment of potential hyperkalemia.[Georgianos and

Agarwal 2018; Weir 2015] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at highest risk to have events (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, poorly controlled diabetes, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

The doses of ALN-AGT01 in this study were selected on the basis of data from the Phase 1 Study 001, in which single ALN-AGT01 doses up to 800 mg were found to have an acceptable safety profile, and clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed after doses as low as 100 mg. Dose selection was guided by the principle of evaluating doses that are well tolerated and predicted to result in a range of PD effects (ie, lowering of serum AGT) and antihypertensive responses. This is expected to enable development of population average dose-response relationships for PD and efficacy to guide identification of optimal treatment regimens (dose and dose frequency) for Phase 3.

Preliminary PK/PD modeling based on serum AGT data from Study 001 indicates that ALN-AGT01 results in a dose-dependent lowering of serum AGT, with maximum reductions predicted to be achieved as early as 1 month postdose and significant reductions sustained for close to 6 months after dosing. Modeling of the relationship between serum AGT lowering and blood pressure suggests a log-linear relationship, with ≥92% reduction in serum AGT predicted to achieve median SBP reduction of ≥10 mmHg.

Based on these, the once every 6 month doses of 150, 300, and 600 mg were selected to result in median serum AGT reductions of 81.9%, 89.4%, and 94.9%, respectively, at trough (Month 6), translating to median SBP reductions of 6.67 mmHg, 8.74 mmHg, and 11.6 mmHg, respectively. Thus, the selected doses will enable characterization of the dose-response relationships for serum AGT and blood pressure with the once every 6 month regimen.

The selected doses also enable characterization of the dose-response relationships for serum AGT and blood pressure with once every 3 month regimens based on analysis of data from all arms at Month 3. This will provide support for development of a once every 3 month regimen, if desired. To this end, 300 mg once every 3 months will be evaluated to identify any cumulative effects. The 300 mg once every 3 months dose is predicted to result in median serum AGT reductions of >95% at trough (Month 3), translating to median SBP reductions of >10 mmHg.

Thus, data from the current study will enable robust characterization of PD and efficacy of once every 3 month and once every 6 month regimens of ALN-AGT01 and guide further development of ALN-AGT01 as an antihypertensive therapeutic that results in reduction of blood pressure by ≥10 mmHg throughout the dosing interval with infrequent administration.

3.4. Method of Assigning Patients to Treatment Groups

Using the Interactive Response Technology (IRT), patients will be randomized 1:1:1:1:1 to the following arms during the first 6 months of the 12-month DB period:

- Placebo SC once every 3 months

- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients initially randomized to placebo will be re-randomized 1:1:1:1 at Month 6 to 1 of the 4 initial ALN-AGT01 regimens.

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period.

Randomization will be stratified by race (black vs all other races) and by baseline blood pressure (mean 24 hour SBP < or ≥145 mmHg).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT system. The Investigator or his/her designee will randomize the patient in IRT after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The Investigator or his/her designee will re-randomize the patient in IRT at Month 6 to assign placebo patients to 1 of the 4 initial ALN-AGT01 dose groups.

3.5. Blinding

The Sponsor, all site personnel (except for the site pharmacist or delegate), and patients will be blinded to study drug treatment through Month 6 of the 12-month DB period. After the database lock to support the analysis of Month 6 data is complete, the Sponsor will be unblinded to treatment assignment, but the site personnel (except for the site pharmacist) and patients will remain blinded to treatment assignment until after the analysis of Month 12 data is complete.

Blinded doses of study drug will be administered under the supervision of the Investigator (see Section 5.2.2). All patients will receive the same volume and number of injections regardless of treatment assignment (patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind). Because ALN-AGT01 may be slightly visually distinguishable from placebo, all blinded study drug doses will be prepared and the syringe(s) will be masked by a site pharmacist or delegate prior to administration by a blinded healthcare professional. See the Pharmacy Manual for additional details.

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 12 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the OLE study.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive
2. Male or female

Patient and Disease Characteristics

3. Has untreated hypertension (not taking antihypertensive medication) or is on stable therapy with 1 or more antihypertensive medications of the following classes: an ACE inhibitor, ARB, renin inhibitor, CCB, thiazide diuretic, and/or thiazide-like diuretic. In general, stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
4. Mean 24-hour SBP ≥135 mmHg and ≤160 mmHg by ABPM, without antihypertensive medication. Patients previously taking medication for hypertension must be without antihypertensives for ≥4 weeks prior to this ABPM.

Informed Consent

5. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Secondary hypertension
2. Orthostatic hypotension (symptomatic or asymptomatic), defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure.

Laboratory Assessments

3. Has any of the following laboratory parameter assessments after at least 4 weeks of washout:
    a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (ULN)
    b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
    d. Elevated potassium >5 mEq/L
    e. eGFR of ≤30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.
5. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the course of the study any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis should be excluded.[Whelton 2018]
6. Currently taking, or taken within 30 days prior to randomization, beta blockers
7. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the course of the study sodium-glucose co-transporter 2 (SGLT2) inhibitors
8. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. In addition, chronic/standing use of over-the-counter NSAIDs is not permitted. Paracetamol/acetaminophen (up to 2 g per day) for analgesia will be allowed.

9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the course of the study
10. Received an RNAi therapeutic (approved or investigational) within 6 months prior to randomization

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor
12. Medical condition, other than hypertension, that requires treatment with a RAAS inhibitor
13. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc
14. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.0%), newly diagnosed Type 2 diabetes mellitus (within 6 months prior to randomization), or laboratory evidence of diabetes during screening (fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], random plasma glucose ≥200 mg/dL [11.1 mmol/L], or HbA1c ≥6.5%) without known diagnosis of diabetes
15. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening
16. Has known human immunodeficiency virus or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
17. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization
18. Clinically significant valvular heart disease
19. New York Heart Association II to IV heart failure
20. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization
21. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
22. History of renal transplantation or under immunosuppressive therapy
23. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient
24. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization
25. Known change in body weight >10% in last 6 months prior to screening

26. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
27. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.7.1
29. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol or Nicotine Use and Substance Abuse

30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
31. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
32. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements

Other Restrictions

33. Third shift or night shift workers
34. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
35. Unable or unwilling to perform HBPM as specified

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.5.2) per Investigator discretion
- AE

- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments and study visits so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug before Month 6 will be encouraged to remain on the study and complete assessments (excluding PK assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until the last patient's Month 6 visit or until PD recovery (whichever is later); see Section 3.1.

Patients who discontinue study drug after the Month 6 visit will be asked to return for their next scheduled visit to complete end of treatment (EOT)/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery; see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be

informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the Month 6 visit assessments at an earlier time (Table 1).

A patient considering stopping participation in the study after the Month 6 visit should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process his/her personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of his/her personal data, informing the study doctor at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-AGT01 SC and placebo SC is provided in the Pharmacy Manual.

5.2.1. Description

ALN-AGT01 will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration).

5.2.2. Dose and Administration

During the 12-month DB period, patients will be administered ALN-AGT01 or placebo, at the same volume and number of SC injections regardless of treatment assignment, once every 3 months. The ALN-AGT01 and placebo groups are below:

- Placebo SC once every 3 months, with re-randomization (1:1:1:1) at Month 6 to 1 of the initial 4 ALN-AGT01 regimens
- 150 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 6 months
- 300 mg ALN-AGT01 SC once every 3 months
- 600 mg ALN-AGT01 SC once every 6 months

Patients who enter the DB Extension period will continue their current blinded dosing regimen from the DB period. Patients receiving once every 6 month ALN-AGT01 regimens will receive placebo SC at dosing visits at which they do not receive ALN-AGT01 to maintain the blind.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, the doses are to be prepared by and syringes are to be masked by an unblinded site pharmacist or designee prior to study drug administration. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. The rotation of sites is recommended. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 42 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a central laboratory as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. If an alternative cause is found, provide appropriate care.
   c. If an alternative cause is not found, perform assessments per Table 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, With No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• May continue study drug dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

Transaminase Level	Action
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparation of ALN-AGT01 or placebo doses according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

ALN-AGT01 will be stored upright and refrigerated at approximately 2 to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of ALN-AGT01 halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.6. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.7. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of ALN-AGT01 supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much ALN-AGT01 is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all ALN-AGT01. Used, partially used, and unused ALN-AGT01 will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the investigational product and its packaging after it is released for distribution at clinical site.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically nonmedical in nature; however, it is possible that investigational product complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, contamination of investigational product, and malfunction of syringe needle safety device.

5.3.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6 instructions on reporting CPCs will also be detailed in the Pharmacy Manual.

5.4. Monitoring for Potential Clinical Events

5.4.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure will be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Low blood pressure that is associated with symptoms should be evaluated at the clinical study site or another hospital setting within 24 hours. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure.
- The Investigator should consider downtitration or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <100 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <110 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the

Investigator, especially if hypotension is noted. Patients will carry Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.

- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) previously started for hypertensive escape should be down-titrated or discontinued.
- The frequency of blood pressure and biochemical monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.
- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for orthostatic intolerance syndromes such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

5.4.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 4.

Table 4: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout Study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe systolic hypertension (office SBP ≥180 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because ALN-AGT01 acts on the RAAS, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as rescue agents for high blood pressure will be avoided throughout this study.

Study Period	Intervention
	• If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Whelton 2018; Williams 2018] • The Investigator should consider downtitration or discontinuation of oral antihypertensives (if taking) if confirmed office SBP <100 mmHg (or <115 mmHg with clinical symptoms such as lightheadedness or dizziness).
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of ALN-AGT01, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic. Investigators should avoid long-acting agents that may not fully washout between Month 5 and Month 6.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic:</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic should be added if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018] • A temporary hold of oral antihypertensives (if taking) will be performed in appropriate patients (below) from Month 5 to Month 6: – Month 5 office SBP <160 mmHg if taking no oral antihypertensive agents – Month 5 office SBP <155 mmHg if taking 1 oral antihypertensive agent – Month 5 office SBP <150 mmHg if taking 2 oral antihypertensive agents. • During this 4-week period, blood pressure will be carefully monitored by daily HBPM and oral antihypertensive medications restarted if confirmed office SBP >170 mmHg (or if confirmed office SBP >160 mmHg accompanied by symptoms)

Study Period	Intervention
Month 6 to End of Study	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, prior oral antihypertensive should be restarted per Investigator judgement if daytime mean SBP is ≥135 mmHg by ABPM. • Oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg; HBPM SBP <135 mmHg; daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

5.4.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial ALN-AGT01 PD. Based upon the renal dysfunction associated with conventional RAAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- Study drug (and additional oral antihypertensive agents, if applicable) should be prophylactically held during intercurrent illness or volume depletion
- If an individual patient experiences a decrease in eGFR by ≥30% from baseline or to ≤30 mL/min/1.73m^2, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypovolemia
  - Urinary infection
  - Urinary tract obstruction
- If an individual patient experiences a decrease in eGFR by ≥40% from baseline or to ≤25 mL/min/1.73m^2, the Investigator should look for potentially reversible causes of renal dysfunction and contact the Sponsor to discuss the potential interruption of study drug. Serum creatinine should be monitored at least weekly until improving.

5.4.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of ALN-AGT01 PD). The following guidelines apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: Recommended Interventions for Hyperkalemia

Serum K^+ ≥5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia.[a] Consider reduction in dose or discontinuation of these agents. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains ≥5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards) • Consider interruption of ALN-AGT01, according to Investigator medical judgment.	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of ALN-AGT01, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer	• Immediately interrupt ALN-AGT01 • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer • Apply all measures outlined for serum K^+ ≥5.5 and < 6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

The availability of patiromer will be assessed at participating study sites. This potassium-binding drug is approved for the treatment of hyperkalemia and has been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.5. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant

medications administered SC, do not administer in same injection site area as the study drug for 4 days after the last dose of study drug.

Occasional use of systemic NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.5.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.5.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.4.2). In addition, after a patient completes the placebo-controlled primary endpoint at Month 3, Investigators will titrate therapy with oral antihypertensives to a target blood pressure range (office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg). All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.5.2. Prohibited Concomitant Medication

The following medications, treatments, and supplements are prohibited throughout the study (until the EOT visit):

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors)
- SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin)
- Prescription NSAIDs
- Chronic/standing use of nonprescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride).

- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.6. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.7. Other Requirements

5.7.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and through safety follow-up (if applicable; Section 3.1).

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently

sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.7.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.7.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements.

5.7.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. Of note, this is the sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.7.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection, are to be performed prior to

dosing at dosing visits. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical study site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs and weight (at the discretion of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/IEC must be signed by the patient or legal guardian before the screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after at least 4 weeks of washout and randomized within the allowed Screening period. Retesting of screening ABPM is permitted once as described in Section 6.2.1, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in Section 10.1.

In patients taking oral antihypertensives, a washout of at least 4 weeks must be completed prior to measurement of the baseline ABPM (for eligibility) and baseline office blood pressure. The baseline ABPM and office blood pressure must be measured within 2 weeks before randomization. An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. HBPM must be collected after at least 4 weeks of

washout for at least 2 consecutive weeks (at least 3 recordings per week) prior to randomization to establish baseline.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.1.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.4.1 and Section 5.4.2, respectively.

6.2.1. ABPM

In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM must be started prior to the morning dose of antihypertensive medication.

Adequacy will be assessed for all ABPMs. If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

See further details in Section 10.1 and the Study Manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.1 and the Study Manual.

6.2.4. Exploratory Wearable Blood Pressure Assessment

Approximately 100 patients at select sites will be given the option of using a wearable blood pressure sensor for 2 periods of 2 to 4 weeks each according to the Schedule of Assessments (Table 1). Wearable blood pressure assessments performed during screening should be obtained

after at least 4 weeks of washout. Participation will be contingent upon individual patient consent. These noninvasive, cuffless devices are worn on the finger or wrist as described in the Study Manual, using the opposite arm as that used for ABPM.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT and RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples collected for AngI and AngII require special processing and will be assessed at sites that have appropriate resources, equipment, and reagents. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Levels of aldosterone will also be analyzed in urine collections at the time points listed in the Schedule of Assessments (Table 1). Blood AGT levels will be analyzed at a central laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. These biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to adjust dosing of ALN-AGT01 or guide other elements of study conduct or clinical management and will not be shared with sites until after study completion. If clinical circumstances arise for which such information is required to guide patient care, local laboratory assessments should be drawn.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma concentrations of ALN-AGT01 and its primary metabolite AS(N-1)3′ ALN-AGT01 at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

Plasma concentrations of ALN-AGT01 and AS(N-1)3′ ALN-AGT01 will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated position, after the patient has rested comfortably for 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and

recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at screening only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks.[Ma 2004] Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.[Ma 2004]

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

When ECG and blood sample collection occur at the same visit, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.5.6.4. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of the assessments all laboratory assessments specified in Table 6 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Blood samples collected for RAAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position).

Spot urine collections for albumin and creatinine should be obtained in the morning. A 24-hour urine collection for aldosterone, sodium, and creatinine will be performed at time points listed in the Schedule of Assessments (Table 1). These 24-hour collections should be obtained within 2 days before the ABPM associated with the same visit.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Hepatitis Tests	
Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBsAg, HBc antibody IgM and IgG
Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin

Fasting glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HbA1c=hemoglobin A1c; HBc=hepatitis B virus core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HDL-C=high-density lipoprotein; HEV=hepatitis E virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LDL-C=low-density lipoprotein; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a central laboratory.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.7.1 for definition of postmenopausal state).

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM, and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen

Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of ALN-AGT01.

An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious adverse events must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up (Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled not to breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose and Other Special Situations Reporting

An overdose is defined as any dose of study drug administered to the participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-AGT01.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). In addition to the dedicated collections for optional exploratory biomarkers (urine, plasma, serum), aliquots from each 24 hour urine collection will be archived for potential exploratory investigations. These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a standard deviation in the range of 15 to 20 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM, a maximum mean difference in effect size between ALN-AGT01 and placebo of 10 mmHg, and a 15% dropout rate at Month 3, a sample size of 375 patients (75 per treatment group) provides at least 84% power to detect a dose response relationship in SBP reduction among all ALN-AGT01 doses and placebo at the 2-sided significance level of 0.05. In addition, this sample size provides at least 80% power to detect a 10 mmHg difference between an individual ALN-AGT01 dose versus placebo with a 2-sided significance level of 0.05. Table 8 shows the statistical power with various standard deviation assumptions.

Table 8: Statistical Power to Detect 10 mmHg Difference Between ALN-AGT01 and Placebo With Various Standard Deviation Assumptions

Assumption of Standard Deviation (mmHg)	Statistical Power to Detect Dose Response Trend (%)	Statistical Power to Detect Difference Between an Individual ALN-AGT01 Dose Versus Placebo (%)
15	97	96
18	90	88
20	84	80

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.

- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 evaluable postdose blood sample for the determination of plasma ALN-AGT01 concentrations.
- **PD Analysis Set**: All patients who received any amount of study drug and who have baseline and at least 1 postdose blood sample for the determination of serum AGT will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. For the efficacy endpoints of change from baseline to Month 3, ALN-AGT01 300 mg once every 3 months and once every 6 months will be pooled together and analyzed. For all other efficacy endpoints, analysis will be performed according to the randomized treatment arm.

Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Subgroup categories and detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change in SBP from baseline at Month 3 assessed by ABPM. The primary hypothesis of the dose response relationship for the primary endpoint across ALN-AGT01 doses and placebo will be tested using a multiple comparison– modeling (MCP Mod) approach.[Bretz 2005] The presence of a dose-response trend will be initially tested against a set of prespecified dose-response models at a 2-sided significance level of 0.05, adjusted for multiplicity (the MCP step). Several candidate models will be prespecified in the SAP. Then, the dose-response curves will be further estimated (the modeling step) based on the 'best' fitted dose response model. Furthermore, each ALN-AGT01 dose group will be compared against placebo using Dunnett's Test.

For the secondary endpoints of change in DBP assessed by ABPM at Month 3 and change in SBP and DBP assessed by ABPM at Month 6, each ALN-AGT01 dose group will be compared with placebo. For change in office SBP and DBP, each ALN-AGT01 dose group will be

compared with placebo at Month 3 and Month 6 and also using the time-adjusted average from Month 1 to Month 3 and from Month 1 to Month 6.

No multiplicity adjustment is applied across primary and secondary endpoints.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD lowering after ALN-AGT01 treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of ALN-AGT01 and its metabolite AS(N-1)3′ ALN-AGT01 will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by SOC and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for

laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during the study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Interim Analysis

The primary analysis will be conducted after all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit. No formal interim analysis is planned before the primary analysis.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be

destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must

also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

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10. APPENDICES

10.1. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) should be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the Study Manual. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP should be used for all subsequent office blood pressure and HBPM readings. The ABPM should be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. In patients taking oral antihypertensives (including those initiated as rescue medication), ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24 hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with adequacy assessment. An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 2 days. If the second ABPM recording is also inadequate during screening, the patient is a screen failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood pressure.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the staff member should leave the room and the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction. If you agree, I would like to leave the room for the next 10 to 15 minutes while it is recording. This will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Using a stopwatch or watch, measure standing blood pressure 1 minute after standing by using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and enter their response in the eCRF.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel who will bring an office blood pressure instrument to the

patient's location and follow the same procedure performed at the site. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used should be entered into the eCRF.

HBPM

Patients should measure HBPM every morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient must measure HBPM for at least 2 consecutive weeks (and with at least 3 successful readings per week) prior to randomization. Patients previously taking medication for hypertension must be without antihypertensives for ≥4 weeks prior to collecting these baseline HBPM measurements. If adequate baseline HBPM data (at least 3 successful readings per week for at least 2 consecutive weeks) are not collected within the Screening period, the patient is a screen failure.

After Day 1, HBPM should be measured at least 3 times per week. Patients may select the 3 days of the week that are most convenient for their personal schedule. The frequency of HBPM monitoring should be increased to daily during the temporary hold of oral antihypertensives performed in some patients from Month 5 to Month 6.