Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Fitzgerald K, White S, Borodovsky A, et al. A highly durable RNAi therapeutic inhibitor of PCSK9. N Engl J Med 2017;376:41-51. DOI: 10.1056/NEJMoa1609243

A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

Authors: Kevin Fitzgerald, Suellen White, Anna Borodovsky, Brian Bettencourt, Andrew Strahs, Valerie Clausen, Peter Wijngaard, Jay Horton, Jorg Taubel, Ashley Brooks, Chamikara Fernando, Robert S. Kauffman, David Kallend, Akshay Vaishnaw, and Amy Simon

CONTENTS

STUDY PERSONNEL 5

SELECTION OF STUDY POPULATION 7

Inclusion Criteria 7
Inclusion Criteria for All Subjects in the Single-dose (SAD) and multiple-dose (MD) Cohorts 7
Additional Inclusion Criteria for Subjects in the SAD and Non-statin MD Cohorts 9
Additional Inclusion Criteria for Subjects in the Statin MD Cohorts 10

Exclusion Criteria 10
Exclusion Criteria for All Subjects in the SAD and MD Cohorts 10
Additional Exclusion Criteria for Subjects in the SAD and Non-statin MD Cohorts 12
Additional Exclusion Criteria for Subjects in the Statin MD Cohorts 13

PCSK9 ASSAY METHODOLOGY 14

SUPPLEMENTARY FIGURES 15

Figure S1. Summary of study design. Panel A, ascending single-dose phase; Panel B, multiple-dose phase. 15

Panel A 17

Panel B 17

Figure S2. Patient flow through the study phases. Panel A, ascending single-dose phase; Panel B, multiple-dose phase. 18

Panel A 18

Panel B 19

SUPPLEMENTARY TABLES 20

Table S1: Baseline and demographic characteristics (Safety population) 20

Table S2: Incidence of the most common (≥5% of total inclisiran subjects) treatment-emergent adverse events in the single ascending dose phase by study treatment (Safety population) 26

Table S3: Incidence of the most common (≥ 10% of total inclisiran subjects) of treatment-emergent adverse events in the multiple dose phase by study treatment (Safety population) 27

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population) 28

Table S5: Least-squares mean (LSM) percent change from baseline (95% CI) (baseline-adjusted ANCOVA model) in pharmacodynamic parameters at day 180 post dose[a] in the single ascending dose phase (Pharmacodynamic population) 34

Table S6 Mean (SD) percent change from baseline in pharmacodynamic parameters at individual and group nadir in the multiple dose phase (Pharmacodynamic population) 36

Table S7: Least-squares mean (LSM) percent change from baseline (95% CI) (baseline-adjusted ANCOVA model) in pharmacodynamic parameters at day 196 post first dose in the multiple dose phase (Pharmacodynamic population) 39

Table S8 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the single ascending dose phase by study treatment (Pharmacodynamic population) 42

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population) 48

Patent reference 55

STUDY PERSONNEL

ALN-PCSsc-001 Study Team Organization		
Affiliation	**Title**	**Name**
Alnylam Pharmaceuticals, Inc.	*Alnylam Medical Monitor, consultant	Robert Kauffman MD
	*Senior Director, Clinical Development/ Medical Monitor	Amy R. Simon, M.D.
	Senior Director, Biometrics	Andrew Strahs
	Associate Director, Biometrics	Brian Bettencourt
	Clinical Operations Manager, consultant	Suellen White
The Medicines Company	*Medical Monitor	David Kallend, MBBS
Richmond Pharmacology, Ltd.	*Principal Investigator	Jorg Taubel, MD, FFPM
	Director of Operations	Keith Berelowitz
	Senior Project Manager	Linh Schram
	Lead Study Manager	Eri Yamamoto
Covance Clinical Research Unit, Leeds	*Principal Investigator	Ashley Brooks MB, CHB
	*Study Medical Monitor and Safety Review Committee Chair	David Blowers MBBS, FFPM
	Project Physician	Chamikara Fernando, MBBS
	Project Manager II: Data Management and Statistical Analyses	Sunee Reiner
	Drug Safety Project Manager	Parveen Kumar
	Senior Clinical Project Manager	Joanne Hodson

ALN-PCSsc-001 Study Team Organization	
Committee	
Safety Review Committee	*Members as noted above include Principal Investigators and Medical Monitors from The Medicines Company, Alnylam and Covance. The Covance Medical Monitor was the committee chair.
Laboratories	
Central Laboratory	**Sample Analysis**
QPS, LLC Newark, Delaware, USA	Pharmacokinetic Analysis
Charles River Laboratories Quebec, Canada	PCSK9 Protein Concentration and Cytokine
Medpace Reference Laboratories Leuven, Belgium	β-Quantification of Total Cholesterol and Low-Density Lipoprotein Cholesterol Exploratory Lipid Biomarker Analysis
Liposcience, Inc. Raleigh, NC USA	Exploratory lipid biomarker: Lipoprotein Profile (Low-Density Lipoprotein Particle)
Local Laboratory	**Sample Analysis**
Covance Clinical Pathology Harrogate and Leeds, UK	Clinical Safety Laboratory Tests
The Doctors Laboratory London, UK	Clinical Safety Laboratory Tests

SELECTION OF STUDY POPULATION

Inclusion Criteria

Inclusion Criteria for All Subjects in the single-dose (SAD) and multiple-dose (MD) Cohorts

To be eligible to participate in the study, all subjects must satisfy the following inclusion criteria.

1. Male and female subjects, aged 18 to 60 years, inclusive; subjects in the multiple dose cohorts may be enrolled up to, and including, age 75 (the upper age limit was adjusted to more accurately reflect the target population, to facilitate enrollment, and to provide pharmacodynamics data for the intended target population).
2. Body mass index (BMI) between 18 and 30 kg/m^2, inclusive
3. Serum LDL-C $\geq$ 2.6 mmol/L ($\geq$ 100 mg/dL) at screening
4. Fasting triglyceride < 4.52 mmol/L (< 400 mg/dL) at screening
5. Adequate complete blood counts (CBCs) (if outside the reference range, CBC values that are not clinically relevant and are acceptable to the Investigator)
6. Female subjects must be of non-childbearing potential:
    - Natural (spontaneous) post-menopausal defined as amenorrhea for 12 months without an alternative medical cause with a screening follicle stimulating hormone (FSH) level > 25 IU/L (or at the local laboratory levels for post-menopause)

- Premenopausal with irreversible surgical sterilization by bilateral oophorectomy or bilateral salpingectomy (with or without hysterectomy), but not tubal ligation, or hysterectomy at least 6 months before screening

7. Male subjects must use acceptable methods of contraception if the male subject's partner could become pregnant from the time of the first administration of study medication until 90 days following administration of the last dose of study medication. One of the following acceptable methods of contraception must be utilized:

   - Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository)
   - Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository)
   - The subject's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository)
   - The subject's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository)

- The subject's female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) must be used
- The subject's female partner has undergone documented placement of an intrauterine device or intrauterine system. In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must be used
- True abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use 1 of the above-mentioned contraceptive methods if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

8. Willing to comply with protocol-required visit schedule and visit requirements and provide written informed consent
9. Non-smokers and non-nicotine users for at least 90 days before screening

Additional Inclusion Criteria for Subjects in the SAD and Non-statin MD Cohorts

1. Healthy as determined by pre-study medical history, physical examination, clinical laboratory assessments, and 12-lead ECG

Additional Inclusion Criteria for Subjects in the Statin MD Cohorts

1. On a stable dose of statin medication for ≥ 30 days before screening with no planned dose change during study participation

Exclusion Criteria

To be eligible to participate in the study, all subjects must not satisfy any of the following exclusion criteria.

Exclusion Criteria for All Subjects in the SAD and MD Cohorts

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical study
2. An underlying known disease, or surgical or medical condition that, in the opinion of the Investigator, might interfere with interpretation of the clinical study results
3. Active serious mental illness or psychiatric disorder, including but not limited to schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention
4. ALT and/or TBIL above the upper limit of normal (ULN); no Investigator discretion and no repeat assessments are allowed, except where otherwise noted (see Section below for an additional criterion for subjects in the MD cohorts)

5. Aspartate aminotransaminase (AST), alkaline phosphatase (ALP), or gamma glutamyl transferase (GGT) > 2×ULN (no Investigator discretion); or, if AST, ALP, or GGT > ULN, but ≤ 2×ULN and considered clinically relevant by the Investigator

6. International normalized ratio (INR) above the upper bound of the normal reference range (as per the local laboratory reference range) at screening

7. Used over-the-counter (OTC) medication, excluding routine vitamins, within 7 days before the first dose of study drug, unless determined by the Investigator and Sponsor to be not clinically relevant, and unlikely to impact blood cholesterol level

8. Received an investigational agent (inclusive of PCSK9 inhibitors) within 90 days before the first dose of study drug or are in follow-up of another clinical study

9. Known hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) infection

10. Clinically significant illness within 7 days before the first dose of study drug

11. Positive screen for alcohol or drugs of abuse

12. Consume more than 14 (female) or 21 (male) units of alcohol per week (unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer)

13. History or clinical evidence of alcohol abuse, within the 12 months before screening. Alcohol abuse is defined as regular weekly intake of more than 21 units for males and 14 units for females (using alcohol tracker at http://www.nhs.uk/Tools/Pages/NHSAlcoholtracker.aspx).

14. History or clinical evidence of drug abuse, within the 12 months before screening. Drug abuse is defined as compulsive, repetitive, and/or chronic use of drugs or other substances with or without problems related to their use and/or where stopping or a reduction in dose will lead to withdrawal symptoms.

15. Donated more than 500 mL of blood within 90 days before the first dose of study drug

16. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or N-acetylgalactosamine (GalNAc)

17. History of intolerance to SC injection or relevant abdominal scarring (surgical, burns, etc.)

18. Any conditions which, in the opinion of the Investigator, would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study

Additional Exclusion Criteria for Subjects in the SAD and Non-statin MD Cohorts

1. History or presence of cardiovascular disease (including peripheral artery and cerebrovascular disease)

2. Systolic blood pressure (SBP) > 140 mmHg and diastolic blood pressure (DBP) > 90 mmHg after 10 minutes supine rest

3. Diagnosis of diabetes mellitus

4. Received any medication or nutraceutical to alter serum lipids within 30 days before screening

5. Used prescription drugs within 14 days or 7 half-lives (whichever is longer) before the first dose of study drug, with the exception of hormone replacement therapy

Additional Exclusion Criteria for Subjects in the Statin MD Cohorts

1. History or presence of CHD, peripheral artery disease, or cerebrovascular disease
2. Uncontrolled hypertension (SBP > 160 mmHg or DBP > 100 mmHg) either on or off antihypertensive treatment on 2 or more occasions before dosing, or controlled BP requiring more than 2 antihypertensive medications
3. Insulin-dependent diabetes mellitus
4. Used prescription drugs within 14 days or 7 half-lives (whichever is longer) before the first dose of study drug, with the exception of statin medication, allowed antihypertensive medication (maximum of 2 per subject), oral hypoglycemic medication, and hormone replacement therapy
5. ALT and/or total bilirubin above the ULN; if ALT and/or total bilirubin is/are elevated at screening, the measurement(s) may be repeated during the screening period and must be within the normal reference range for subject continuation

PCSK9 ASSAY METHODOLOGY

PCSK9 was measured using a validated ELISA method (Quantikine ELISA PCSK9 kit, Catalog no. DPC900, R&D Systems, Minneapolis, MN) at Charles River Laboratories Montreal ULC, Senneville, QC, Canada. The assay had an analytical lower limit of quantitation (LLOQ) of 0.63 ng/mL, and samples were diluted 1/20 for analysis (giving a 12.6 ng/mL functional LLOQ). The assay intra-assay co-efficient of variation (CV) ranged from 0.4–23.4% CV, while the inter-assay variability ranged from 1.8–11.0% CV across the quality control standards and the lower and upper limits of quantitation. Intra-assay accuracy ranged from 93.8 to 118.2%, and inter-assay accuracy ranged from 98.9 to 110.1%.

SUPPLEMENTARY FIGURES

Figure S1. Summary of study design. Panel A, ascending single-dose phase; Panel B, multiple-dose phase.

The starting dose for subjects in SAD Cohort 1 was 25 mg Inclisiran (or placebo). Progression to subsequent SAD dose levels was contingent on SRC review of postdose safety, tolerability, and available PD data from all subjects from the previous cohort(s). Progression from the SAD phase to the first cohort in the MD phase was contingent upon selection of 1 or more doses deemed safe and tolerable following SRC review of postdose safety, tolerability, and available PD data from all subjects in at least the first 3 SAD cohorts. Two dose levels were selected in the MD phase and planned for administration to 2 cohorts; the same dose was administered to subjects in a non-statin cohort and to subjects in a statin cohort. In addition to the planned cohorts (4 SAD and 4 MD cohorts), the protocol permitted the enrollment of up to 2 optional cohorts in both the SAD and MD (either on or off statins co-medication) phases. Three of these 4 optional cohorts were enrolled, including 1 cohort in the SAD phase to expand the 800 mg inclisiran cohort and 2 cohorts in the MD phase that examined alternative dose regimens (weekly [QW] and biweekly [Q2W] regimens) in subjects who were not on statin co-medication. Exploration of alternate dose regimens was permitted per the adaptive design criteria.

In both SAD and MD, subjects underwent “Extended PD Follow-up” if at day 84 after the last study treatment, their latest three LDL-C measurements averaged <80% of baseline. That follow-up continued until 180 days after the last study treatment or the

time when the latest three LDL-C measurements averaged ≥80% of baseline, whichever came sooner.

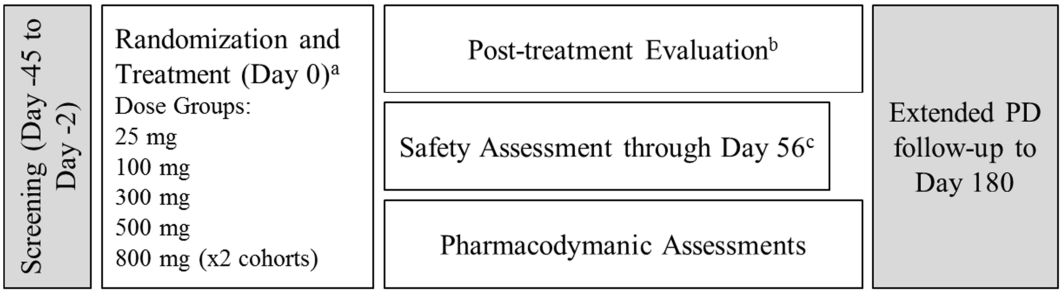
Dosing for QWx4 cohorts: Days 0, 7, 14, 21

Dosing for Q2Wx2 cohort: Days 0 and D14

Dosing for QMx2 cohort: Days 0 and D 28

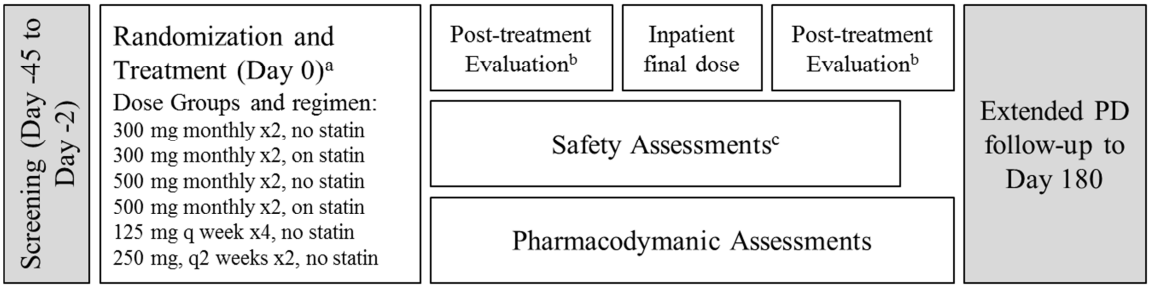
D = study day, i.e., day relative to day of first study treatment; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamics; SAE = serious adverse events

Panel A



[a] Subjects were admitted to clinic on Day -1, randomized and dosed on Day 0, discharged on Day 1
[b] Study Days 1, 2, 4, 7, 14, 21, 28, 35, 42, 56, 70, 84
[c] After Day 56, only SAEs were collected

Panel B



[a] Subjects were admitted to clinic on Day -1, randomized and dosed on Day 0, discharged on Day 1, for all regimens.
[b] Study Days:

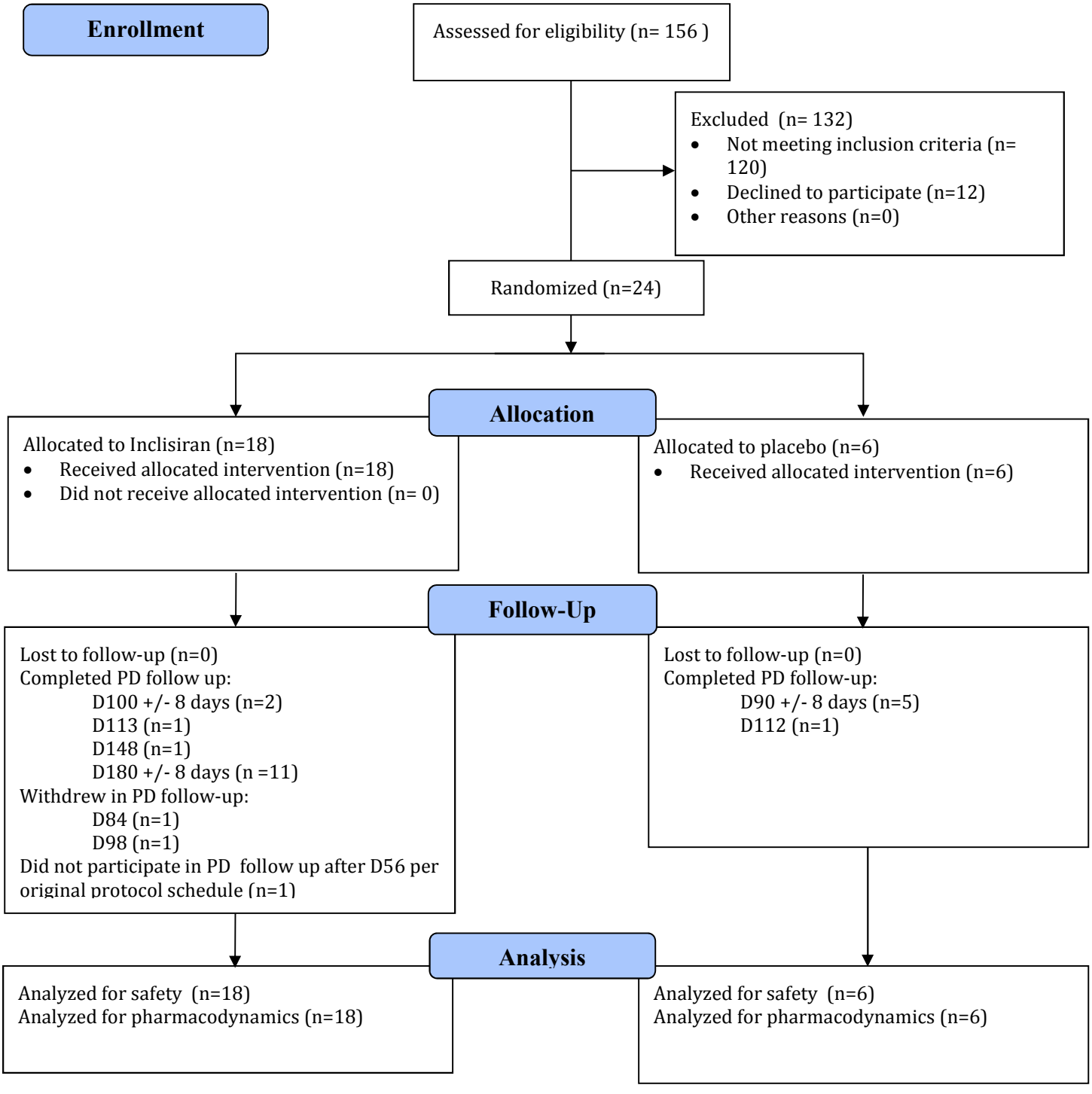
- Monthly regimen: Day 2, 4, 7, 14, 21, 27 to 29*, 35, 42, 56, 63, 70, 84, 98, 112
- Weekly regimen: Day 2, 4, 7, 14, 20 to 22*, 28, 35, 49, 56, 63, 77, 91, 105
- Biweekly regimen: Day 2, 4, 7, 13 to 15* 21, 28, 35, 42, 49, 56, 70, 84, 98
  *inpatient stay for final dose

[c] After Day 70, 77, or 84 for biweekly, weekly, or monthly regimen respectively, only SAEs were collected

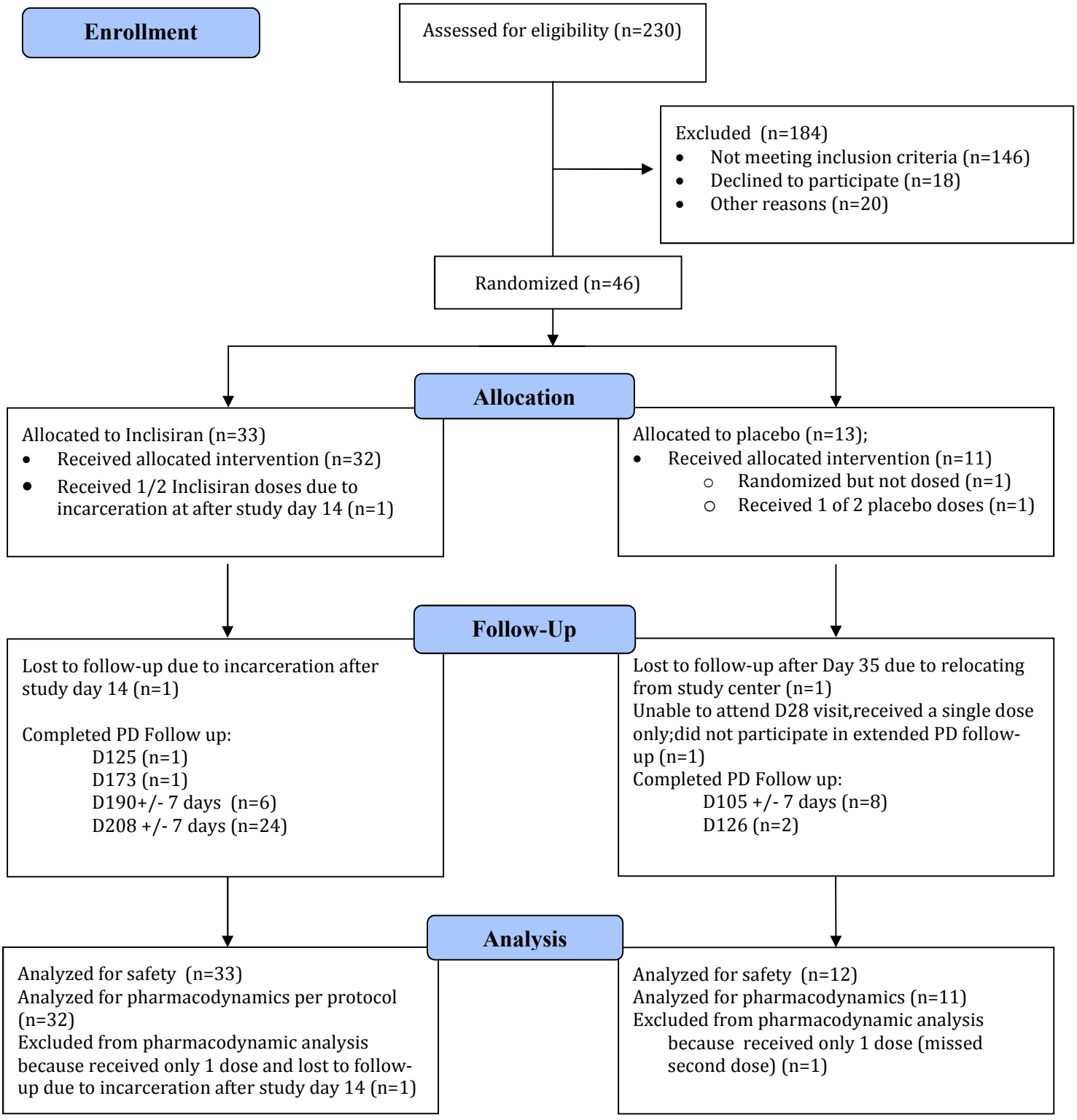
Figure S2. Patient flow through the study phases. Panel A, ascending single-dose phase; Panel B, multiple-dose phase.

D = study day, i.e., day relative to day of first study treatment; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamics;

Panel A



Panel B


Enrollment
Assessed for eligibility (n=230)
Excluded (n=184)
Not meeting inclusion criteria (n=146)
Declined to participate (n=18)
Other reasons (n=20)
Randomized (n=46)
Allocation
Allocated to Inclisiran (n=33)
Received allocated intervention (n=32)
Received 1/2 Inclisiran doses due to incarceration at after study day 14 (n=1)
Allocated to placebo (n=13);
Received allocated intervention (n=11)
Randomized but not dosed (n=1)
Received 1 of 2 placebo doses (n=1)
Follow-Up
Lost to follow-up due to incarceration after study day 14 (n=1)
Completed PD Follow up:
D125 (n=1)
D173 (n=1)
D190+/- 7 days (n=6)
D208 +/- 7 days (n=24)
Lost to follow-up after Day 35 due to relocating from study center (n=1)
Unable to attend D28 visit,received a single dose only;did not participate in extended PD follow-up (n=1)
Completed PD Follow up:
D105 +/- 7 days (n=8)
D126 (n=2)
Analysis
Analyzed for safety (n=33)
Analyzed for pharmacodynamics per protocol (n=32)
Excluded from pharmacodynamic analysis because received only 1 dose and lost to follow-up due to incarceration after study day 14 (n=1)
Analyzed for safety (n=12)
Analyzed for pharmacodynamics (n=11)
Excluded from pharmacodynamic analysis because received only 1 dose (missed second dose) (n=1)

SUPPLEMENTARY TABLES

Table S1: Baseline and demographic characteristics (Safety population)

	Single ascending dose phase							Multiple dose phase								
		Inclisiran						Placebo		Inclisiran						
	Placebo (n=6)	25 mg (n=3)	100 mg (n=3)	300 mg (n=3)	500 mg (n=3)	800 mg (n=6)	Overall (n=24)	With Statin (n=4)	No Statin (n=8)	300 mg QMx2 With Statin (n=4)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)	Overall (n=45)
Age, years																
Mean	48	47	48	48	39	49	47	58	51	52	47	56	42	55	61	52
(SD)	(14.2)	(14.2)	(6.2)	(12.7)	(14.0)	(6.7)	(10.7)	(3.0)	(14.2)	(21.6)	(8.7)	(11.5)	(16.1)	(9.4)	(6.3)	(12.7)
Sex, n (%)																
Male	2	3	3	3	3	5	19	2	6	2	6	2	3	4	4	29
	(33.3%)	(100%)	(100%)	(100%)	(100%)	(83.3%)	(79.2%)	(50.0%)	(75.0%)	(50.0%)	(100%)	(40.0%)	(50.0%)	(66.7%)	(66.7%)	(64.4%)
Race, n (%)																
White	4	2	3	1	3	3	16	4	7	3	6	3	5	5	3	36
	(66.7%)	(66.7%)	(100%)	(33.3%)	(100%)	(50.0%)	(66.7%)	(100%)	(87.5%)	(75.0%)	(100%)	(60.0%)	(83.3%)	(83.3%)	(50.0%)	(80.0%)

Table S1: Baseline and demographic characteristics (Safety population)

	Single ascending dose phase							Multiple dose phase								
		Inclisiran						Placebo		Inclisiran						
	Placebo (n=6)	25 mg (n=3)	100 mg (n=3)	300 mg (n=3)	500 mg (n=3)	800 mg (n=6)	Overall (n=24)	With Statin (n=4)	No Statin (n=8)	300 mg QMx2 With Statin (n=4)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)	Overall (n=45)
Black or African American	2 (33.3%)	1 (33.3%)	0	1 (33.3%)	0	0	4 (16.7%)	0	0	0	0	1 (20.0%)	0	0	1 (16.7%)	2 (4.4%)
Asian	0	0	0	1 (33.3%)	0	1 (16.7%)	2 (8.3%)	0	0	1 (25.0%)	0	1 (20.0%)	1 (16.7%)	1 (16.7%)	0	4 (8.9%)
Other	0	0	0	0	0	2 (33.3%)	2 (8.3%)	0	1 (12.5%)	0	0	0	0	0	2 (33.3%)	3 (6.7%)
Body weight, kg																
Mean	70.6	84.5	77.3	81.2	71.6	74.0	75.5	74.3	77.6	85.0	77.8	71.9	64.9	73.1	83.2	75.8
(SD)	(12.04)	(2.11)	(6.66)	(11.04)	(7.93)	(6.01)	(9.16)	(5.07)	(10.31)	(22.04)	(15.19)	(11.03)	(7.86)	(7.07)	(8.12)	(12.03)

Table S1: Baseline and demographic characteristics (Safety population)

	Single ascending dose phase							Multiple dose phase							
		Inclisiran						Placebo		Inclisiran					
	Placebo (n=6)	25 mg (n=3)	100 mg (n=3)	300 mg (n=3)	500 mg (n=3)	800 mg (n=6)	Overall (n=24)	With Statin (n=4)	No Statin (n=8)	300 mg QMx2 With Statin (n=4)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)	Overall (n=45)
Height, cm																
Mean	168	175	174	173	175	169	172	168	171	176	175	167	168	167	176	171
(SD)	(10.6)	(2.3)	(5.1)	(9.6)	(3.1)	(5.5)	(7.2)	(10.5)	(9.3)	(12.5)	(7.4)	(11.7)	(5.3)	(6.9)	(10.1)	(9.2)
BMI, kg/m^2																
Mean	24.9	27.7	25.5	27.0	23.4	25.9	25.6	26.5	26.7	27.1	25.2	25.7	23.0	26.2	27.0	25.9
(SD)	(3.17)	(0.21)	(2.10)	(1.29)	(3.01)	(1.60)	(2.39)	(2.72)	(2.64)	(3.59)	(2.95)	(1.97)	(2.34)	(2.72)	(1.93)	(2.72)
LDL-C, mg/dL																
Mean	131.5	177.9	150.8	162.4	119.9	158.5	146.9	143.1	131.5	143.1	143.1	104.4	123.7	139.2	146.9	135.3
(SD)	(19.3)	(50.7)	(35.6)	(36.7)	(17.0)	(28.6)	(32.9)	(89.7)	(20.9)	(30.5)	(20.1)	(19.7)	(49.9)	(18.6)	(14.3)	(35.6)
TG, mg/dL																
Mean	70.9	115.1	177.1	132.9	159.4	115.1	124.0	150.6	124.0	132.9	132.9	97.4	88.6	88.6	159.4	124.0
(SD)	(12.4)	(59.3)	(102.7)	(48.7)	(84.1)	(21.3)	(57.6)	(46.9)	(38.1)	(86.8)	(90.3)	(44.3)	(20.4)	(25.7)	(69.1)	(58.5)

Table S1: Baseline and demographic characteristics (Safety population)

	Single ascending dose phase							Multiple dose phase							
		Inclisiran						Placebo		Inclisiran					
	Placebo (n=6)	25 mg (n=3)	100 mg (n=3)	300 mg (n=3)	500 mg (n=3)	800 mg (n=6)	Overall (n=24)	With Statin (n=4)	No Statin (n=8)	300 mg QMx2 With Statin (n=4)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)	Overall (n=45)
PCSK9																
Mean	278.95	342.65	233.77	253.82	263.23	279.62	276.32	460.69	276.23	460.69	311.47	433.44	288.07	380.03	288.73	348.34
(SD), µg/L	(99.53)	(67.89)	(39.17)	(22.36)	(24.98)	(66.90)	(68.28)	(56.295)	(58.69)	(209.435)	(59.85)	(107.28)	(69.07)	(50.63)	(53.53)	(103.99)
Concomitant statin use	0	0	0	0	0	0	0	4 (100%)	0	4 (100%)	0	5 (100%)	0	0	0	13[a] (28.9%)
ATV	0	0	0	0	0	0	0	0	0	4[b] (100%)	0	3[c] (60.0%)	0	0	0	7 (15.6%)
SIM	0	0	0	0	0	0	0	3[d] (75.0%)	0	0	0	2[e] (40.0%)	0	0	0	5 (11.1%)
PRV	0	0	0	0	0	0	0	1[f] (25.0%)	0	0	0	0	0	0	0	1 (2.2%)
Amlodipine	0	0	0	0	0	0	0	0	0	1 (25.0%)	0	0	0	0	0	1 (2.2%)

Table S1: Baseline and demographic characteristics (Safety population)

	Single ascending dose phase							Multiple dose phase							
		Inclisiran						Placebo		Inclisiran					
	Placebo (n=6)	25 mg (n=3)	100 mg (n=3)	300 mg (n=3)	500 mg (n=3)	800 mg (n=6)	Overall (n=24)	With Statin (n=4)	No Statin (n=8)	300 mg QMx2 With Statin (n=4)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)	Overall (n=45)
Candesartan	0	0	0	0	0	0	0	0	0	1 (25.0%)	0	0	0	0	0	1 (2.2%)
Perindopril erbumine	0	0	0	0	0	0	0	1 (25.0%)	0	0	0	0	0	0	0	1 (2.2%)

ATV = atorvastatin; BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; PRV = pravastatin; SIM = simvastatin; QMx2 = 2 monthly doses; QWx4 = 4 weekly doses; Q2Wx2 = 2 biweekly doses; SD = standard deviation; TG = triglycerides.

To convert values for cholesterol to mmol/L divide by 38.67. To convert values for TG to mmol/L divide by 88.57.

[a]11 subjects reported being on statin for approximately 1–9 years, 2 subjects for <4 months before study drug administration

[b]2 subjects 40 mg, 1 subject 20 mg, 1 subject 10 mg

[c]2 subjects 40 mg, 1 subject 20 mg

[d]All subjects 40 mg

[e]1 subject 40 mg, 1 subject 20 mg

[f]1 subject 20 mg

Table S2: Incidence of the most common (≥5% of total inclisiran subjects) treatment-emergent adverse events in the single ascending dose phase by study treatment (Safety population)

		Inclisiran					
Preferred Term	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**	**Total (N=18)**
At least 1 TEAE, n (%)	2 (33.3%)	2 (66.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	4 (66.7%)	9 (50.0%)
Cough	0	0	1 (33.3%)	0	1 (33.3%)	0	2 (11.1%)
Musculoskeletal pain	0	1 (33.3%)	0	0	0	1 (16.7%)	2 (11.1%)
Nasopharyngitis	0	1 (33.3%)	0	1 (33.3%)	0	0	2 (11.1%)

TEAE = treatment-emergent adverse event.

Table S3: Incidence of the most common (≥ 10% of total inclisiran subjects) of treatment-emergent adverse events in the multiple dose phase by study treatment (Safety population)

	Placebo			Inclisiran						
Preferred Term	With Statin (n=4)	No Statin (n=8)	Total (n=12)	300 mg QMx2 With Statin (N=4)	300 mg QMx2 No Statin (N=6)	500 mg QMx2 With Statin (N=5)	500 mg QMx2 No Statin (N=6)	125 mg QWx4 No Statin (N=6)	250 mg Q2Wx2 No Statin (N=6)	Total (n=33)
At least 1 TEAE, n (%)	4 (100%)	5 (62.5%)	9 (75.0%)	3 (75.0%)	2 (33.3%)	5 (100%)	4 (66.7%)	5 (83.3%)	5 (83.3%)	24 (72.7%)
Headache	1 (25.0%)	1 (12.5%)	2 (16.7%)	1 (25.0%)	1 (16.7%)	0	2 (33.3%)	1 (16.7%)	1 (16.7%)	6 (18.2%)
Back pain	1 (25.0%)	1 (12.5%)	2 (16.7%)	0	0	1 (20.0%)	3 (50.0%)	1 (16.7%)	0	5 (15.2%)
Diarrhea	1 (25.0%)	2 (25.0%)	3 (25.0%)	1 (25.0%)	0	1 (20.0%)	0	2 (33.3%)	0	4 (12.1%)
Naso-pharyngitis	0	1 (12.5%)	1 (8.3%)	0	0	1 (20.0%)	0	1 (16.7%)	3 (50.0%)	5 (15.2%)

QMx2 = 2 monthly doses; QWx4 = 4 weekly doses; Q2Wx2 = 2 biweekly doses; TEAE = treatment-emergent adverse event.

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
PCSK9						
Day 84						
Mean (SD) percent change	-0.1 (14.3)[a]	-47.3 (7.2)[b]	-29.9 (12.9)	-72.6 (12.1)	-68.7 (9.8)	-72.2 (8.5)
Day 180						
Mean (SD) percent change	NA	NA	-15.7 (0.2)[b]	-47.8 (24.8)	-70.3 (6.6)[b]	-74.3 (13.2)[c]
Mean (SD) percent change at individual nadir[d]	-29.4 (9.53)	-54.3 (4.75)	-48.9 (27.37)	-77.9 (3.49)	-75.7 (11.75)	-82.3 (4.85)

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Mean (SD) percent change at group nadir[e]	-17.5 (19.56)	-51.2 (0.56)	-41.7 (21.28)	-74.0 (0.57)	-77.7 (1.28)	-79.4 (3.27)
Time to group nadir, days	35	42	42	42	112	98
LDL-C						
Day 84						
Mean (SD) percent change	-7.5 (15.6)[a]	-27.9 (11.4)[b]	-36.6 (6.1)	-48.4 (19.0)	-47.6 (15.2)	-41.9 (12.3)[a]

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Day 180						
Mean (SD) percent change	NA	NA	-26.3 (2.1)[b]	-47.8 (0.5)	-37.9 (21.7)[b]	-35.2 (16.8)[c]
Mean (SD) percent change at individual nadir[d]	-18.7 (5.61)	-34.5 (8.62)	-42.9 (15.35)	-55.0 (10.03)	-55.1 (19.93)	-59.2 (12.25)
Mean (SD) percent change at group nadir[e]	-8.6 (18.07)	-27.9 (11.43)	-38.7 (2.07)	-48.4 (18.99)	-55.1 (24.46)	-51.8 (8.44)
Time to group nadir, days	98	84	140	84	98	35
Total cholesterol						
Day 84	-1.3 (11.7)	-20.2 (9.4)	-18.2 (10.7)	-30.9 (9.4)	-24.2 (10.2)	-28.1 (11.7)

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Day 180	NA	NA	-14.1 (2.9)	-30.5 (5.7)	-23.5 (11.1)	-25.0 (12.2)
HDL-C						
Day 84	11.7 (14.4)	8.3 (10.3)	19.6 (17.7)	50.5 (71.3)	6.5 (6.4)	1.9 (17.0)
Day 180	NA	NA	18.1 (26.3)	12.8 (42.5)	-2.8 (2.8)	-0.2 (16.4)
non-HDL-C						
Day 84	-6.6 (12.2)	-25.5 (11.3)	-28.8 (7.5)	-47.2 (19.2)	-34.1 (12.6)	-36.0 (12.6)
Day 180	NA	NA	-21.2 (3.6)	-38.0 (12.6)	-29.5 (13.6)	-30.4 (13.4)

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo	**25 mg**	**100 mg**	**300 mg**	**500 mg**	**800 mg**
	(n=6)	**(n=3)**	**(n=3)**	**(n=3)**	**(n=3)**	**(n=6)**
Apolipoprotein B						
Day 84	-10.0 (15.6)	-18.2 (9.7)	-28.1 (15.6)	-45.5 (20.5)	-36.0 (11.7)	-44.5 (11.8)
Day 180	NA	NA	-30.5 (7.6)	-37.6 (12.2)	-29.2 (18.8)	-27.7 (13.6)
Triglycerides						
Day 84	-12.4 (7.9)	-9.0 (19.7)	-9.6 (20.2)	-25.1 (29.2)	15.1 (28.1)	24.6 (48.2)
Day 180	NA	NA	-18.7 (35.5)	45.0 (105.8)	-8.6 (10.1)	-7.4 (23.2)
Lipoprotein (a)						
Day 84	6.7 (25.7)	-2.8 (29.0)	-20.1 (3.5)	-33.8 (46.7)	-30.4 (27.0)	-22.1 (20.8)

Table S4: Mean (SD) percent change from baseline in pharmacodynamic parameters in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Day 180	NA	NA	6.6 (23.7)	-37.9 (35.8)	-31.1 (26.7)	-2.5 (18.9)

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; PCSK9 = proprotein convertase subtilisin/kexin type 9; SD = standard deviation.

[a]n=5

[b]n=2

[c]n=4

[d]Individual nadir values defined as the largest post-dose percent reduction from baseline value per subject. These values were then summarized.

[e]Group nadir is defined as the largest mean post-dose percent change from baseline value during the study.

Table S5: Least-squares mean (LSM) percent change from baseline (95% CI) (baseline-adjusted ANCOVA model) in pharmacodynamic parameters at day 180 post dose[a] in the single ascending dose phase (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
PCSK9	NA	NA	-12.7[b] (-43.3,34.2)	-51.8 (-66.3,-31.2)	-70.1[b] (-80.6,-53.8)	-75.3[c] (-81.8,-66.6)
LDL-C	NA	NA	-23.6[b] (-42.9,2.2)	-47.0 (-58.4,-32.5)	-40.5[b] (-55.7,-19.9)	-36.4[c] (-48.3,-21.9)
Total cholesterol	NA	NA	-10.5[b] (-29.4,13.4)	-30.6 (-41.9,-17)	-26.0[b] (-41.1,-7.2)	-26.3[c] (-36.9,-13.9)
HDL-C	NA	NA	13.3[b] (-25.7,72.7)	2.9 (-27.7,46.6)	6.2[b] (-32.9,68.1)	-1.0[c] (-26.3,33)
non-HDL-C	NA	NA	-18.1[b] (-34.8,2.9)	-37.9 (-48.6,-24.9)	-30.2[b] (-44.6,-12.1)	-31.4[c] (-41.6,-19.4)
Apolipoprotein B	NA	NA	-27.0[b] (-53,13.3)	-38.6 (-54.2,-17.6)	-33.3[b] (-55.9,0.8)	-28.9[c] (-44.9,-8.2)
Lipoprotein (a)	NA	NA	3.5[b] (-47.4,103.9)	-43.7 (-67.3,-3.2)	-34.4[b] (-66.4,28.1)	-2.8[c] (-39.8,57.1)

ANCOVA = analysis of covariance; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LSM = least-squares mean; NA = not applicable; PCSK9 = proprotein convertase subtilisin/kexin type 9.

[a]p-values were not generated for comparison of values at Day 180

[b]n=2

[c]n=4

Table S6 Mean (SD) percent change from baseline in pharmacodynamic parameters at individual and group nadir in the multiple dose phase (Pharmacodynamic population)

	Placebo		Inclisiran					
			300 mg QMx2	300 mg QMx2	500 mg QMx2	500 mg QMx2	125 mg QWx4	250 mg Q2Wx2
	With Statin (n=3)	No Statin (n=8)	With Statin (n=3)	No Statin (n=6)	With Statin (n=5)	No Statin (n=6)	No Statin (n=6)	No Statin (n=6)
PCSK9								
Mean (SD) percent change at individual nadir[a]	-42.4 (3.76)	-25.3 (20.51)	-86.1 (2.06)	-80.4 (4.92)	-88.5 (3.67)	-81.5 (5.73)	-83.8 (2.13)	-82.7 (2.81)
Mean (SD) percent change at group nadir[b]	-21.2(8.9)	-6.1 (NC)	-83.6 (4.06)	-73.1 (6.31)	-85.2 (1.83)	-79.9 (5.35)	-80.3 (4.73)	-79.4 (3.83)

Table S6 Mean (SD) percent change from baseline in pharmacodynamic parameters at individual and group nadir in the multiple dose phase (Pharmacodynamic population)

	Placebo		Inclisiran					
			300 mg QMx2	300 mg QMx2	500 mg QMx2	500 mg QMx2	125 mg QWx4	250 mg Q2Wx2
	With Statin (n=3)	No Statin (n=8)	With Statin (n=3)	No Statin (n=6)	With Statin (n=5)	No Statin (n=6)	No Statin (n=6)	No Statin (n=6)
Time to group nadir, days	28	91	56	56	84	84	77	35
LDL-C								
Mean (SD) percent change at individual nadir[a]	-27.7 (13.19)	-19.2 (9.68)	-53.8 (19.78)	-64.4 (13.22)	-59.9 (18.14)	-56.2 (14.59)	-52.1 (4.75)	-60.4 (11.02)
Mean (SD) percent change at group nadir[b]	-18.4 (17.7)	-16.3 (NC)	-46.7 (18.29)	-55.7 (13.20)	-48.9 (23.77)	-51.9 (14.97)	-44.8 (4.07)	-54.8 (7.77)

Table S6 Mean (SD) percent change from baseline in pharmacodynamic parameters at individual and group nadir in the multiple dose phase (Pharmacodynamic population)

	Placebo		Inclisiran					
			300 mg QMx2	300 mg QMx2	500 mg QMx2	500 mg QMx2	125 mg QWx4	250 mg Q2Wx2
	With Statin (n=3)	No Statin (n=8)	With Statin (n=3)	No Statin (n=6)	With Statin (n=5)	No Statin (n=6)	No Statin (n=6)	No Statin (n=6)
Time to group nadir, days	35	105	70	70	140	140	63	49

LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; QMx2 = 2 monthly doses; QWx4 = 4 weekly doses; Q2Wx2 = 2 biweekly doses; SD = standard deviation.

[a]Individual nadir values defined as the largest post-dose percent reduction from baseline value per subject. These values were then summarized.

[b]Group nadir is defined as the largest mean post-dose percent change from baseline value during the study.

Table S7: Least-squares mean (LSM) percent change from baseline (95% CI) (baseline-adjusted ANCOVA model) in pharmacodynamic parameters at day 196 post first dose in the multiple dose phase (Pharmacodynamic population)

	Placebo (pooled for statin and no statin) (n=11)	Inclisiran					
		300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin[a] (n=6)	250 mg Q2Wx2 No Statin[a] (n=6)
PCSK9	NA	-73.5[b]	-67.7	-77.6[c]	-79.2	-71.6	-70.2
		(-81.9,-61.1)	(-74.2,-59.7)	(-83,-70.6)	(-83.4,-74.1)	(-77.2, -64.5)	(-76.1,-62.8)
LDL-C	NA	-40.3[b]	-47.2	-50.2[c]	-45.5	-38.4	-44.0
		(-64.2,-0.3)	(-60.7,-29.1)	(-65.3,-28.6)	(-59.4,-27)	(-50.4,-23.6)	(-58.5,-24.5)
Total cholesterol	NA	-19.9[b]	-30.3	-27.4[c]	-24.6	-22.0	-27.3
		(-33.4,-3.6)	(-37.6,-22.1)	(-36.7,-16.8)	(-32.6,-15.6)	(-30.3,-12.8)	(-35,-18.8)

Table S7: Least-squares mean (LSM) percent change from baseline (95% CI) (baseline-adjusted ANCOVA model) in pharmacodynamic parameters at day 196 post first dose in the multiple dose phase (Pharmacodynamic population)

	Placebo (pooled for statin and no statin) (n=11)	Inclisiran					
		300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin[a] (n=6)	250 mg Q2Wx2 No Statin[a] (n=6)
HDL-C	NA	10.5[b]	-3.3	8.2[c]	3.9	4.4	9.3
		(-4.3,27.5)	(-11,5.2)	(-2.3,19.8)	(-4.4,12.9)	(-3.9,13.5)	(0.5,18.7)
non-HDL-C	NA	-29.2[b]	-38.6	-42.2[c]	-37.7	-33.2	-38.2
		(-45.7,-7.7)	(-47.7,-27.9)	(-52.5,-29.7)	(-47,-26.8)	(-43.1,-21.5)	(-47.3,-27.4)
Apolipoprotein B	NA	-24.8[b]	-36.1	-39.5[c]	-31.4	-28.0	-38.2
		(-42.4,-1.7)	(-45.5,-25.1)	(-50.1,-26.5)	(-41.5,-19.6)	(-38.6,-15.7)	(-47.2,-27.5)
Lipoprotein (a)	NA	-18.3[b]	-12.9	-32.0[c]	-17.0	-10.8	-29.8
		(-45.7,22.9)	(-31.9,11.5)	(-50.9,-5.9)	(-34.5,5.2)	(-32.9,18.5)	(-40.2,-17.7)

ANCOVA = analysis of covariance; CI= confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LSM = least-squares mean; NA = not applicable; PCSK9 = proprotein convertase subtilisin/kexin type 9; QMx2 = 2 monthly doses; QWx4 = 4 weekly doses; Q2Wx2 = 2 biweekly doses.

[a]Day 189 for 125 mg QWx4 group and day 194 for 250 mg Q2Wx2 group; 196 days post first dose for all dose regimens; p-values were not generated for comparison of values at Day 196 post-dose

[b]n=2

[c]n=4

Table S8 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the single ascending dose phase by study treatment (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
LDL-C						
Baseline						
Mean (SEM), mg/dL	142.3 (11.4)	184.1 (27.0)	162.0 (16.1)	173.6 (29.5)	135.3 (3.3)	161.6 (10.2)
Day 84						
Mean (SEM), mg/dL	137.3 (13.4)[a]	147.7 (0.4)[b]	101.3 (5.0)	91.6 (11.4)	70.8 (11.9)	137.3 (21.4)[a]
Day 180						
Mean (SEM), mg/dL	NA	NA	130.7 (2.3)[b]	90.5 (15.3)	64.2[c]*	105.6 (15.3)[d]

Table S8 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the single ascending dose phase by study treatment (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
At group nadir[a]						
Mean (SEM), mg/dL	118.3 (2.9)[b]	147.7 (0.4)[b]	108.7 (1.5)[b]	89.3 (21.4)	62.6 (24.6)[b]	77.7 (7.3)
Total cholesterol						
Baseline						
Mean (SEM), mg/dL	216.9 (15.9)	266.4 (31.1)	244.8 (20.6)	242.1 (18.7)	222.7 (6.2)	237.0 (10.2)
Day 84						
Mean (SEM), mg/dL	223.1 (18.8)[a]	230.9 (4.6)[b]	198.0 (6.1)	166.3 (12.2)	167.8 (8.8)	179.0 (10.9)

Table S8 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the single ascending dose phase by study treatment (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Day 180						
Mean (SEM), mg/dL	NA	NA	224.3 (12.0)[b]	167.0 (9.1)	172.9 (11.6)[b]	177.2 (15.0)[d]
Non-HDL-C						
Baseline						
Mean (SEM), mg/dL	157.8 (11.1)	214.2 (34.8)	194.9 (28.1)	201.1 (25.0)	165.5 (11.1)	186.4 (11.1)
Day 84						
Mean (SEM), mg/dL	153.1 (14.5)[a]	177.5 (7.9)[b]	137.3 (16.7)	106.3 (24.9)	107.5 (5.6)	117.9 (9.8)

Table S8 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the single ascending dose phase by study treatment (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Day 180						
Mean (SEM), mg/dL	NA	NA	173.0 (25.1)[b]	123.7±17.1	120.0 (6.6)[b]	131.9 (11.8)[d]
HDL-C						
Baseline						
Mean (SEM), mg/dL	59.6 (5.3)	52.2 (4.3)	49.9 (7.8)	41.0 (9.3)	57.2 (4.9)	50.7 (3.6)
Day 84						
Mean (SEM), mg/dL	70.0 (6.6)[a]	53.8 (3.5)[b]	60.7 (12.8)	59.6 (15.7)	60.3 (3.2)	51.4 (4.6)
Day 180						

Table S8 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the single ascending dose phase by study treatment (Pharmacodynamic population)

		Inclisiran				
	Placebo (n=6)	**25 mg (n=3)**	**100 mg (n=3)**	**300 mg (n=3)**	**500 mg (n=3)**	**800 mg (n=6)**
Mean (SEM), mg/dL	NA	NA	51.0 (13.1)[b]	43.7 (8.4)	52.2 (5.0)[b]	45.2 (3.8)[d]
Apolipoprotein B						
Baseline						
Mean (SEM), mg/dL	96.0 (8.7)	132.0 (19.3)	131.0 (21.7)	125.0 (13.9)	101.6 (6.3)	121.0 (6.3)
Day 84						
Mean (SEM), mg/dL	92.0 (10.4)[a]	118.0 (9.0)[b]	91.0 (11.1)	67.0 (13.5)	64.0 (3.5)	75.0 (3.4)
Day 180						
Mean (SEM), mg/dL	NA	NA	105.0 (20.0)[b]	78.0 (12.4)	74.0 (8.5)[b]	88.0 (5.6)[d]

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Non-HDL-C = non-high-density lipoprotein cholesterol (total cholesterol – HDL-C); SEM = standard error of the mean.

[a]n=5

[b]n=2

[c]n=1

[d]n=4

Baseline comprises the average of all measurements before the first study treatment. For subsequent measurement times, where only one measurement is available, that measurement is presented; where only two are available, they are presented as a minimum–maximum range.

Where no data are given, subjects no longer met protocol criteria for extended pharmacodynamic follow up.

To convert values for cholesterol to mmol/L divide by 38.67; to convert values for apolipoprotein B to g/L divide by 100.

* SEM not calculated due to insufficient sample size.

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population)

	Placebo		Inclisiran					
	With Statin (n=3)	No Statin (n=8)	300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)
LDL-C								
Baseline								
Mean (SEM), mg/dL	152.0 (41.6)	134.2 (9.2)	146.2 (13.7)	145.8 (12.9)	131.5 (11.2)	131.9 (20.2)	150.4 (7.6)	129.5 (10.2)
Day 84[a]								
Mean (SEM), mg/dL	150.8 (43.8)	111.8 (4.8)[b]	81.2 (8.7)	61.9 (10.2)	65.4 (10.5)	68.4 (18.5)	93.2 (8.4)	65.0 (11.0)
Day 196[c]								
Mean (SEM), mg/dL	NA	NA	94.4 (6.0)[d]	80.0 (10.3)	66.5 (15.1)[e]	75.0 (17.9)	94.4 (9.3)	77.0 (13.5)

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population)

	Placebo		Inclisiran					
	With Statin (n=3)	No Statin (n=8)	300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)
At group nadir								
Mean (SEM), mg/dL	NA	89.3[f]*	75.0 (10.1)	63.4 (9.2)	60.3 (17.4)	65.7 (17.4)	83.5 (5.9)	59.6 (7.9)
Total cholesterol								
Baseline								
Mean (SEM), mg/dL	237.4 (52.6)	220.4 (11.3)	227.0 (22.3)	219.6 (13.5)	214.6 (15.8)	206.5 (16.7)	243.2 (10.0)	227.4 (11.2)
Day 84[a]								
Mean (SEM), mg/dL	240.9 (49.0)	192.6 (9.4)[b]	168.6 (4.8)	132.6 (11.4)	152.0 (14.5)	152.7 (14.6)	183.7 (10.6)	149.7 (10.7)

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population)

	Placebo		Inclisiran					
	With Statin (n=3)	No Statin (n=8)	300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)
Day 196[c]								
Mean (SEM), mg/dL	NA	NA	171.7 (13.5)[d]	154.7 (12.8)	148.9 (18.3)[e]	158.2 (15.5)	188.7 (11.9)	166.3 (13.2)
Non-HDL-C								
Baseline								
Mean (SEM), mg/dL	190.6 (53.6)	160.9 (12.1)	172.9 (29.0)	171.7 (12.6)	149.7 (10.9)	145.8 (20.0)	182.1 (11.4)	174.8 (11.8)
Day 84[a]								
Mean (SEM), mg/dL	50.5 (87.4)	138.4 (8.2)[b]	108.3 (6.4)	77.3 (11.6)	82.4 (9.3)	85.1 (19.3)	115.6 (11.1)	96.3 (8.9)

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population)

	Placebo		Inclisiran					
	With Statin (n=3)	No Statin (n=8)	300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)
Day196[c]								
Mean (SEM), mg/dL	NA	NA	123.4 (14.9)[d]	107.9 (12.7)	84.7 (13.7)[e]	95.1 (19.5)	124.9 (16.3)	109.4 (11.4)
HDL-C								
Baseline								
Mean (SEM), mg/dL	46.8 (2.9)	59.2 (5.6)	54.1 (10.0)	48.0 (4.5)	65.0 (6.8)	60.7 (7.8)	61.1 (9.6)	52.6 (7.2)
Day 84[a]								
Mean (SEM), mg/dL	51.4 (1.8)	54.1 (7.7)[b]	59.9 (10.4)	55.3 (7.3)	69.2 (10.2)	67.7 (8.0)	68.1 (10.2)	53.4 (3.1)

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population)

	Placebo		Inclisiran					
	With Statin (n=3)	No Statin (n=8)	300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)
Day 196[c]								
Mean (SEM), mg/dL	NA	NA	48.7 (1.5)[d]	47.2 (4.7)	64.6 (6.3)[e]	63.0 (8.4)	63.8 (9.9)	56.8 (6.0)
Apolipoprotein B								
Baseline								
Mean (SEM), mg/dL	119.0 (32.0)	96.0 (7.0)	111.0 (18.6)	113.0 (7.7)	87.0 (5.1)	93.0 (10.1)	108.0 (7.0)	96.0 (8.1)
Day 84[a]								
Mean (SEM), mg/dL	110.0 (29.3)	82.0 (5.5)[b]	68.0 (4.5)	55.0 (7.0)	52.0 (5.3)	52.0 (10.0)	72.0 (5.5)	54.0 (7.9)

Table S9 Mean (SEM) absolute lipid level (mg/dL) over the follow-up period of the multiple dose phase by study treatment (Pharmacodynamic population)

	Placebo		Inclisiran					
	With Statin (n=3)	No Statin (n=8)	300 mg QMx2 With Statin (n=3)	300 mg QMx2 No Statin (n=6)	500 mg QMx2 With Statin (n=5)	500 mg QMx2 No Statin (n=6)	125 mg QWx4 No Statin (n=6)	250 mg Q2Wx2 No Statin (n=6)
Day 196[c]								
Mean (SEM), mg/dL	NA	NA	86.0 (14.5)[d]	74.0 (7.8)	57.0 (8.5)[e]	66.0 (11.0)	79.0 (7.9)	63.0 (9.9)

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Non-HDL-C = non-high-density lipoprotein cholesterol (total cholesterol – HDL-C); QMx2 = 2 monthly doses; QWx4 = 4 weekly doses; Q2Wx2 = 2 biweekly doses; SEM = standard error of the mean.

Baseline comprises the average of all measurements before the first study treatment.

Where no data are given, subjects no longer met protocol criteria for extended pharmacodynamic follow up.

[a]Day 91 for 125 mg QWx4 group;; 84 days post first dose for all other dose regimens

[b]n=6

[c]Day 189 for 125 mg QWx4 group and day 194 for 250 mg Q2Wx2 group; 196 days post first dose for all other dose regimens;

[d]n=2

[e]n=4

[f]n=1

* SEM not calculated due to insufficient sample size.

To convert values for cholesterol to mmol/L divide by 38.67; to convert values for apolipoprotein B to g/L divide by 100.

Patent Reference

Inclisiran is described in US Patent Application Publication Number US2016/0017335 (PCSK9 iRNA COMPOSITIONS AND METHODS OF USE THEREOF) and is listed as sequence AD-60212.