A randomised, double-blind, placebo controlled, first-in-human study to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic response of SLN360 in subjects with elevated lipoprotein(a)

Protocol status: Protocol Amendment 3

Date: 09 Nov 2021

Protocol version: 6.0_09Nov2021

Investigational product: SLN360

Protocol reference number: SLN360-001

EudraCT Number: 2020-002471-35

Sponsor:

Silence Therapeutics plc
72 Hammersmith Road
London W14 8TH
UK

Sponsor signatory:

Dr Daniel Swerdlow MD PhD

Senior Medical Director

DocuSigned by:
E5C9194CA9BA46E...

Signature

09-Nov-2021 | 9:46 AM GMT

Date

Lead Investigator signatory:

Dr Steven Nissen MD MACC

Chief Academic Officer, Heart and Vascular Institute

Cleveland Clinic

DocuSigned by:
Steven Nissen
CD0A0A78B78148D...

Signature

09-Nov-2021 | 7:20 AM PST

Date

Protocol signature page for Investigators

Protocol title:

A randomised, double-blind, placebo controlled, first-in-human study to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic response of SLN360 in subjects with elevated lipoprotein(a)

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SLN360-001

Confidentiality and Current Good Clinical Practice (E6(R2) Compliance Statement):

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), Good Clinical Practice, and relevant International Council for Harmonisation guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Silence Therapeutics including, but not limited to, the current Investigator's Brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Silence Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Silence Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or parties assisting me with the study are adequately qualified and informed about the Silence Therapeutics study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and study records that include all pertinent observations on each of the site's study subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subject's state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Silence Therapeutics to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

Name: _____

Title: _____

Institution: _____

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Contents

1 Introduction

1.1 OVERVIEW

The investigational medicinal product (IMP) SLN360 is being developed by Silence Therapeutics for the treatment of patients with conditions associated with raised lipoprotein(a) (Lp(a)), including aortic stenosis (AS), coronary artery disease (CAD) and peripheral artery disease.

Lp(a) is significant because it is the major carrier of oxidized phospholipid (OxPL) in human plasma.[1] OxPLs are mediators of potent proatherogenic and proinflammatory effects and are thought to account for a significant proportion of the cardiovascular risk attributable to Lp(a).[2] Critically, variants in *LPA*, the gene encoding apolipoprotein(a) (apo(a)),which genetically determine increased plasma Lp(a) levels and apo(a) isoform size) strongly associate with OxPL-apolipoprotein B (apoB) concentration.[3]

Elevated Lp(a) is an independent, direct and causal risk factor for atherothrombotic cardiovascular disease (CVD), particularly CAD. Mendelian randomisation studies show that a genetically determined doubling of Lp(a) plasma levels results in a 22% increased risk of myocardial infarction (MI), consistent with a causal relationship between lifelong elevation in Lp(a) and MI.[4] *LPA* risk alleles (i.e. those determining elevated Lp(a) levels) have been linked with other atherosclerotic adverse outcomes, including ischemic stroke, peripheral artery disease, abdominal aortic aneurysm, obstructed coronary vessels (i.e. coronary atherosclerotic burden) and earlier onset of CAD.[5,6] Importantly, extremely elevated Lp(a) (>180 mg/dL) have a very elevated lifetime risk of atherosclerotic CVD equivalent to the risk associated with heterozygous familial hypercholesterolemia.[7] Patients with AS whose circulating Lp(a) levels are in the upper third of the Lp(a) distribution (>35 mg/dL; >88 nmol/L) exhibit increased valvular calcification activity compared with those in the lowest two thirds, and

patients in the upper third of the Lp(a) distribution show a median ~3-fold more rapid progression in aortic valve calcium burden and faster annualized hemodynamic progression, with an associated higher event rate (aortic valve replacement procedures and all-cause mortality).[1]

SLN360 is a 19-mer double-stranded small interfering RNA (siRNA) targeting *LPA* messenger RNA (mRNA). SLN360 drug substance is produced solely by chemical synthesis. The manufacture of SLN360 drug product does not involve excipients derived from human or animal origin. *LPA* encodes apo(a), a protein specific to the Lp(a) particle. Apo(a) is dominant and rate-limiting in the synthesis of Lp(a). The SLN360 siRNA molecule is covalently linked to a tri-antennary N-acetyl-galactosamine (GalNAc) moiety via a novel linker. The GalNAc residues of SLN360 bind specifically to the asialoglycoprotein receptor (ASGPR) which is expressed specifically on hepatocytes. Thus, these modifications ensure that SLN360 is targeted specifically to hepatocytes. Following binding and receptor-mediated cellular uptake by endocytosis, *LPA* mRNA is then targeted for degradation via RNA interference by the antisense strand of the siRNA. Through its highly specific silencing of *LPA* in hepatocytes, SLN360 is designed to reduce apo(a) levels, thereby reducing plasma Lp(a) levels. It is anticipated that this reduction in Lp(a) levels will reduce the risk of CVD. In large randomised trials, PCSK9 inhibitor drugs reduced Lp(a) by ~26%,[8,9] and reduction of CVD event risk was greater in patients with elevated Lp(a).[8]

Targeting a major component of the atherogenic Lp(a) particle through RNA interference is a novel approach and is expected to address significant unmet medical need associated with increased Lp(a), without the limitations and toxicities of currently available therapies.

1.2 SUMMARY OF NON-CLINICAL PHARMACOLOGY

The SLN360 siRNA sequence was selected and its potency confirmed by examining the in vitro inhibition of *LPA* mRNA in the human RT-4 cell line after transfection with the unconjugated siRNAs. For clinical use the siRNA must be made resistant to degradation by chemical modification and targeted to the hepatocytes by conjugation with GalNAc via a linker. The potency of the chemically modified and GalNAc conjugated siRNA was confirmed by in vitro inhibition of *LPA* mRNA in primary hepatocytes of cynomolgus monkeys and humans. Additionally, there was no activity of the lead molecule, STS20041L6 on the closely related off-target gene for plasminogen (*PLG*) in primary hepatocytes of both species. The lead sequence subsequently underwent optimization and the final configuration of SLN360 was identified.

An in vivo pharmacokinetic (PK)/pharmacodynamic (PD) study was performed in female cynomolgus monkeys using STS20041L6. A single subcutaneous (s.c.) dose at 3.0 or 9.0 mg/kg led to a significant and prolonged reduction of target *LPA* gene expression in the liver, with levels reduced by 60% and 85% at 6 weeks post-dose, respectively. Repeated s.c. treatment with 3.0 mg/kg showed 88% reduction 6 weeks after final dosing. No effect on *APOB* or *PLG* mRNA was observed over the measurement period, demonstrating that unwanted *PLG* knockdown is not a concern.

The reduction in *LPA* mRNA levels resulted in significant reductions in peak 85% and 95% reductions following 3.0 or 9.0 mg/kg, respectively. Nine weeks after dosing, serum levels were still reduced by approximately 50% and 88%, respectively compared to baseline levels. Repeated dosing with 3.0 mg/kg resulted in a maximal decrease in serum Lp(a) of >95% 1 week after the final dose (Day 21), which was maintained until the experiment was terminated on Day 63.

Determination of the minimally effective dose (MED) was performed in a second PK/PD experiment using male cynomolgus monkeys. The MED was identified as 0.3 mg/kg, with an ED_{50} at 0.6 mg/kg following analysis 29 days after a single dose of SLN360. Both 1.0 and 3.0 mg/kg induced a sustained reduction of serum Lp(a), such that on Day 29 serum Lp(a) levels were reduced by 46% compared to baseline following injection at 1.0 mg/kg and 81% following injection at 3.0 mg/kg.

Following a second s.c. administration on Day 29, a reduction in all groups was noted. Animals receiving 0.1 and 0.3 mg/kg showed a transient decrease in serum Lp(a) levels, peaking on Day 36 at 19% and 35% respectively. In contrast, there was a marginal increase in the peak reduction of serum Lp(a) in both the 1.0 mg/kg (65% compared to baseline levels on Day 57) and 3.0 mg/kg (90% compared to baseline levels on Day 50) groups. A greater than 50% reduction was maintained at Day 64 in the 1.0 mg/kg and Day 85 in the 3.0 mg/kg dosed animals. Following multiple dosing, animals dosed with 0.3 mg/kg showed a reduction to 34% compared to baseline levels on Day 29. Animals dosed with 1 mg/kg showed a marked and sustained reduction in Lp(a) serum levels, peaking at 82% reduction compared with baseline levels on Day 22, maintaining greater than 50% reduction until Day 71. These results identify the MED of SLN360 as 0.3 mg/kg. Sustained reduction of serum Lp(a) levels can be achieved through dosing with 1.0 or 3.0 mg/kg.

No adverse clinical observations, injection site reactions (ISRs) or changes in clinical chemistry or coagulation parameters were observed in either in vivo study at pharmacological doses.

The series of in vivo studies in naïve animals therefore confirm the anticipated PD changes which would be expected from specific inhibition of *LPA* mRNA expression.

1.3 SUMMARY OF TOXICOLOGY

Repeat dose toxicology studies have been conducted for SLN360. The *LPA* gene is restrictively expressed across species. A recent Basic Local Alignment Search Tool (BLAST) search of the human *LPA* mRNA shows that the expression of *LPA* is restricted to humans, great apes and old-world monkeys (BLAST search performed on sequence NM_005577.4 on 7th October 2019). The basis for selecting the non-human primate (NHP), therefore, lies primarily with the expression of the target *LPA* sequence, which is specifically expressed in NHPs and in humans, and thus provides the only possibility to investigate target-specific toxicological effects of SLN360. SLN360 is pharmacologically active in the cynomolgus monkey.

Rats were included to understand any potential liabilities that are unrelated to the on-target effects of the molecule, including any potential unidentified off-target effects or those associated with chemical modifications within the molecule.

In a dose-range finding (DRF) non-Good Laboratory Practice (GLP) study in male and female Sprague Dawley rats, once-weekly (3 doses) s.c. administration of 30, 100, or 200 mg/kg SLN360 was clinically well tolerated over 16 days. Reductions in body weight gain noted for both sexes and had no effect on the clinical condition of the animals. Expected microscopic changes (dose-dependent) for this class of molecule[10] were noted in the liver (including fatty change characterised by hepatocellular vacuolation with increased single cell necrosis, increased mitoses and bile duct hyperplasia) and in the kidney (tubular vacuolation, tubular necrosis and basophilic granules), correlating with clinical pathology changes (increased liver enzymes, creatinine and urea).

In a GLP study in male and female Sprague Dawley rats, once-weekly (5 doses) s.c. administration of 3, 10 or 30 mg/kg SLN360 to male and female rats over 29 days with an 8-week recovery was clinically well tolerated. Non-adverse, expected, reversible hepatocyte and kidney tubule vacuolation was observed, the no-observed-adverse-effect level (NOAEL) was at least 30 mg/kg.

In a DRF non-GLP study in male and female cynomolgus monkeys, once-weekly (3 doses) s.c. administration of 30, 100 or 200 mg/kg SLN360 to male and female monkeys over 16 days was clinically well tolerated, with no adverse findings.

In a GLP study in male and female cynomolgus monkeys, once-weekly (five doses) s.c. administration of 30, 100, or 150/200 mg/kg SLN360 to male and female monkeys over 29 days with an 8 week recovery was clinically well tolerated. Non-adverse reversible increased liver weight with diffuse

hepatocyte hypertrophy (minimal to slight) and non-adverse reversible vacuolated macrophages in lymph nodes was observed, the NOAEL was at least 200 mg/kg.

SLN360 has been shown to be non-genotoxic in a panel of genotoxicity assays (in vitro Ames assay, mouse lymphoma assay and human lymphocyte micronucleus assay and in vivo rat micronucleus assay) and to have no effect on the assessed safety pharmacology end-points (hERG outward tail current, CNS function in the rat and monkey repeat dose GLP studies, and respiratory rate and cardiovascular function [hemodynamics, heart rate and electrocardiography] in the monkey repeat dose GLP toxicity study).

1.4 SUMMARY OF NON-CLINICAL PHARMACOKINETICS

In pharmacology studies, single s.c. doses of STS20041L6 at 3.0 and 9.0 mg/kg in the cynomolgus monkey showed more than dose proportional increases in the maximum serum concentration (C_{max}) and area under the curve over the measurement period of 24 h (AUC_{0-24}). C_{max} was achieved at 2 to 4 hours post-dose and there was no accumulation following repeat dosing at 3.0 mg/kg. STS20041L6 was rapidly eliminated, such that 80–90% of drug was cleared after 8 h. Single s.c. doses of SLN360 at 0.1, 0.3, 1.0 and 3.0 mg/kg resulted in dose proportional increases in C_{max} and AUC_{0-24}. C_{max} was achieved at 1-2 hours post-dose, with rapid clearance (only the 3.0 mg/kg group had detectable levels of SLN360 24 hours post dose).

The tissue distribution of SLN360 was explored over 21 days in male and female Wistar rats (plasma, blood cell pellet, whole blood, liver, kidney, lungs, spleen, heart, bone marrow, testes, ovary, uterus and thymus), following a single 10 mg/kg s.c. injection. SLN360 was detected at significant tissue concentrations in liver (peaked at 6 hours, declining at 24 hours) and kidney (plateau around 6 hours post-dose, starting to decline after 72 hours) while levels in other organs were extremely limited, with no marked blood cell uptake or binding. These findings are consistent with the GalNAc siRNA delivery system.[10]

In the rat studies, 15-day dose range finding and 29-day GLP study, SLN360 toxicology was similar. In the GLP study in male and female Sprague Dawley rats, following once-weekly (five doses) s.c. administration of SLN360 at 3, 10, or 30 mg/kg, sex differences in SLN360 C_{max} and AUC_{0-48} values were evident on repeat dosing, with higher exposure (approximately 2-fold) observed in males compared to females. Exposure, as assessed by SLN360 C_{max} and AUC_{0-48} values, increased with the increase in SLN360 dose level from 3 to 30 mg/kg/week. The increases in SLN360 C_{max} and AUC_{0-48} values were greater than proportional to dose, indicative of a saturable clearance process. Liver and kidney exposure increased with dose, with kidney exposure higher than that observed in the liver.

In the cynomolgus monkey studies, 15-day dose range finding and 29-day GLP study, SLN360 toxicology was similar, albeit with slightly higher exposure in males compared to females in the 15-day study. In the cynomolgus monkey 29-day GLP study, following once-weekly (five doses) s.c. administration of SLN360 at 30, 100, or 150/200 mg/kg, SLN360 was rapidly absorbed and after reaching C_{max}, SLN360 concentrations declined rapidly, with individual $t_{1/2}$ values ranging from 2.42 to 5.88 hours on day 1 in males and females. Sex ratios for dose normalized mean SLN360 C_{max} and AUC_{0-20} values were close to unity (range 0.764-1.39). Exposure, as assessed by dose normalized mean SLN360 C_{max} and AUC_{0-20} values, increased with each increase in nominal dose level between 30 and 150 or 200 mg/kg/week. The observed increases in exposure were dose proportional to the increases in actual dose level. No accumulation of SLN360 in plasma was observed after five once-weekly subcutaneous doses in cynomolgus monkeys.

1.5 ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (ADME)

SLN360 is very stable in cynomolgus monkey and human hepatic lysosomes and following incubation with rat, cynomolgus monkey and human hepatic S9 (post-mitochondrial supernatant fraction). SLN360 is a protein bound in plasma from the rat (>96.2%), cynomolgus monkey (>97.5%) and man (>94%).

In terms of potential Cytochrome P450 (CYP) interactions, SLN360 is not a potent inducer of CYP1A2, CYP2B6 or CPY3A4 or an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19 or CYP2D6 in human hepatocytes. SLN360 is not an inhibitor of the P-gp and BCRP transporters or a substrate for the P-gp, BCRP, OAT1, OAT3, OCT2 or MATE2-K transporters.

SLN360 exhibited inhibitory potential for CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP2B6 and CYP3A4/5 in suspended or plated human hepatocytes with the half maximal inhibitory concentration (IC_{50}) values greater than or equal to 12 µM. Clinical exposure is expected to be much lower than 12 µM, so this potential inhibition is considered to not be clinically significant.

1.6 IMMUNOGENICITY

To assess the potential for anti-drug antibodies (ADAs) against SLN360, SLN360 was coupled to a carrier protein (*Limulus polyphemus* hemolymph hemocyanin), formulated in adjuvant and injected into rabbits intramuscularly on six separate occasions (1 mg/kg [dose 1], 0.5 mg/kg [doses 2–5], 0.25 mg/kg [dose 6]) over a period of 16 weeks. No specific antibodies to SLN360 were generated, suggesting the risk of ADA formation is minimal.

1.7 STUDY RATIONALE

The preclinical pharmacology data support the use of SLN360 in subjects with raised Lp(a). The principal aim of this study is to obtain safety and tolerability data when SLN360 is administered subcutaneously as single and multiple doses to subjects. This information, together with the PD and PK data, will help determine the safe, well tolerated active dose(s) and define the dosing regimen of SLN360 suitable for future clinical studies.

The current clinical study aims to generate an early safety assessment and demonstrate initial proof-of-concept data in humans via the measurement of key serum biomarkers.

1.8 BENEFIT-RISK ASSESSMENT

1.8.1 Background and rationale

SLN360 is a candidate siRNA medicine for the treatment of patients with conditions associated with raised Lp(a). SLN360 has the potential to address a major unmet medical need in this target subject population through targeted reduction of apo(a), a key component of the atherogenic Lp(a) particle.

This phase 1 study will employ a starting dose of 30 mg with appropriate safeguards, including a Safety Review Committee (SRC). A comprehensive communication plan will be employed to facilitate rapid suspension of dosing in the event of safety concerns. Furthermore, sentinel dosing will be employed during the single ascending dose (SAD) part of the study.

1.8.2 Unmet medical need

There are no approved specific therapeutics designed to potently lower Lp(a). Existing lipid-lowering therapies either have limited (proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors), neutral or even an adverse impact (statins) on Lp(a).[11,12] Lp(a) is a prevalent genetic risk factor for onset and progression of several manifestations of CVD.[13]

Meta-analyses have identified associations between continuous Lp(a) concentrations and risk of CAD even when adjusting for other lipids and established risk factors, including increased risk of non-fatal MI and coronary death from ~Lp(a) >30 mg/dL.[14] Genome-wide association studies have identified the *LPA* locus as the most strongly associated with risk of coronary disease, with two variants (rs10455872 and rs3798220)—both highly associated with increased plasma Lp(a), reduced *LPA* copy number (i.e.

reduced kringle IV type 2 repeats) and smaller Lp(a) particle size—associated with an odds ratio for CAD of 1.51 for one variant and 2.57 for two or more variants.[15]

There are multiple mechanisms by which Lp(a) might play a role in CVD beyond those attributable to low-density lipoprotein (LDL). The mechanisms behind the atherogenic properties of Lp(a) have been reviewed extensively.[16,17] These can be summarized as follows: as with all apoB-containing lipoproteins <70 nm in diameter, Lp(a) can activate and freely flux across the endothelial barrier - particularly in the setting of endothelial dysfunction - where it can be retained within the arterial wall.[18] Lp(a) has a higher affinity for endothelial cell and extracellular matrix compared to LDL. While both LDL and Lp(a) can permeate vascular endothelium[19], the apo(a) component of Lp(a) also enables it to bind to exposed lysine residues on vascular endothelium.[20] This binding facilitates uptake by macrophages, resulting in foam-cell formation and, ultimately, atherosclerotic plaque formation. The similarity to plasminogen may allow Lp(a) to interfere with fibrinolysis and plasmin activation, resulting in pro-thrombotic activities. Lp(a) is also highly inflammatory due to its OxPL load, and promotes lipid deposition, endothelial dysfunction and osteogenic differentiation to induce monocyte trafficking to the arterial wall.[18] As a corollary, elevated Lp(a) in humans has been associated with greater plaque vulnerability,[21] and increased arterial inflammation in association with an activated, inflammatory monocyte phenotype favoring endothelial adherence and transmigration.[18]

1.8.3 Dose justification

The potential of SLN360 to reduce the expression of systemic Lp(a) has been demonstrated in NHP models. Doses of up to 9.0 mg/kg have been shown to significantly reduce systemic Lp(a) in NHP models for periods of up to 9 weeks, without any detrimental effects being observed.

Based on studies in cynomolgus monkeys, the minimal effective dose is 0.3 mg/kg, 1/10th of the active dose. It is assumed that there will be a 1:1 translation from NHP to human based on modelling data, showing that the PD effect in both humans and NHPs is predicted to be the same. Assuming there is a 1:1 translation from NHP to human, it is expected that doses will have to account for subjects with a bodyweight of up to 100 kg, translating to a starting dose of 30 mg. Based on the modelling data, this dose is anticipated to reduce Lp(a) by approximately 20% for 1-month post-dose. This reduction of 20% is considered to be an acceptable minimal effect level for entry into clinical testing. Reduction in Lp(a) will be monitored during the dose escalation and accumulated Lp(a) data will support the dose escalation decision for each step in the first-in-human study. The SLN360 exposure will be monitored to ensure that for the proposed dose range of 30 – 900 mg, the exposure in humans does not exceed that observed at the NOAEL.

In the cynomolgus monkey (chosen for dose selection as it is considered the most relevant species pharmacologically and toxicologically), the NOAEL was 100 mg/kg (13-week repeat dose study). The human-equivalent dose (HED) of this NOAEL was calculated using the United States Food and Drug Administration's (FDA) 2005 guideline, "Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers", as below:
Cynomolgus monkey NOAEL in the 13-week repeat dose study: 100 mg/kg
HED: 100/3.1 = 32.26 mg/kg
Applying 10×safety margin: 32.26/10 = 3.23 mg/kg
Converting to a 60 kg human: 3.23 x 60 = 193.80 mg
This study begins dosing at 30 mg which is significantly below the 193.80 mg calculated using the FDA formula. Additionally, minimal effective dose studies suggest that this 30mg dose will likely achieve a modest PD effect. Therefore, a 30 mg starting dose is conservative and suitable from a safety perspective, whilst having some pharmacological activity so as to best produce data of value.

PK exposure limits have also been calculated based on cynomolgus monkey data at the NOAEL, and a 10-fold safety factor has also been applied. The limits are C_{max} 3650 ng/ml, and AUC_{0-168} 83,700 h*ng/ml.

The extent and duration of Lp(a) suppression after a single dose of SLN360, along with safety and PK data, will guide the dosing interval for the multiple dose (MD) part of the study. The target therapeutic dose will aim to achieve >70% suppression Lp(a) over a at least a 4-week dosing interval, with the objective of reducing as far as possible the burden, for the patient, of drug administration.

1.8.4 Study design

For the SAD part of the study, a sequential-group, ascending-dose design has been chosen for safety reasons, since SLN360 is in the early stages of clinical development. The study will include a full review of the accumulated clinical laboratory data and any safety reports prior to dose escalation. An optional cohort may be added to evaluate an intermediate dose level or to repeat a dose cohort to better understand the impact of SLN360 at a particular dose and its suitability for use in the MD part of the study.

Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration. Based upon the non-clinical data, the duration of each treatment period is considered adequate to achieve the study objectives.

1.8.5 Use of placebo

This study will be placebo controlled and double-blinded in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related. Furthermore, placebo is used since no appropriate active comparator is available.

1.8.6 Potential risks and risk management

This study has been designed to recognize potential risks to subjects. The eligibility criteria and screening procedures are designed to exclude subjects who may be at undue risk if they participate in the study.

Markers of liver injury and kidney function and routine haematology markers along with adverse events (AEs) will be assessed frequently during the study (see Appendix 5: Schedule of Assessments) and by the SRC for each dose escalation to evaluate any longitudinal trends in AEs.

1.8.7 Contraception, pregnancy and women of child-bearing potential

Women of child-bearing potential (WOCBP) will be required to use highly effective contraception, further described below, for the duration of their exposure to SLN360 and for a period of 3 months following the last administration of SLN360. The inclusion of WOCBP on effective contraception is appropriate since treatment with SLN360 to reduce Lp(a) has potential to reduce risk of Lp(a)-related adverse disease outcomes throughout adulthood.

1.8.8 Injection site reactions

As SLN360 and placebo are administered subcutaneously; the protocol includes assessment of ISRs using an accepted rating scale and these possible reactions will be recorded as AEs.

1.8.9 Overdose

From a primary pharmacology perspective, the subjects are individuals who have elevated Lp(a) levels. The majority of the general population of European ancestry has low (<50mg/dL) levels of circulating Lp(a).[4] These low levels are not associated with adverse health outcomes, and individuals with no detectable Lp(a) have been identified who display no detrimental effects.[22,23] Therefore, potential harmful effects of significantly reduced Lp(a) levels are not expected to be a primary concern, and

exaggerated primary pharmacology is not expected to occur. Since SLN360 is administered in a controlled clinical setting by healthcare professionals the potential for overdose is extremely low. The Sponsor will collect information pertinent to overdose across the clinical development program. Further information regarding overdose will be provided by the Sponsor to Investigators in the Investigator's Brochure (IB).

1.8.10 Drug-drug interactions

Based on preclinical pharmacology and in vitro and in silico modelling, preliminary data from in vitro studies suggest that SLN360 is not recognized by the CYP P450 enzyme system and is not an inducer or inhibitor of the metabolic enzyme pathway at pharmacologically relevant exposure. The potential for drug-drug interactions is therefore very low. This will, however, be further investigated as the clinical development program evolves.

1.8.11 Anaphylaxis

As with all novel medications the risk of anaphylaxis has not yet been established in man. Subjects will be admitted as inpatients for at least 24 hours following administration of SLN360 in close proximity to resuscitation facilities in order to observe them in this critical period, when anaphylactic potential is highest. Furthermore, clinical stopping rules will ensure the study can be paused or stopped should anaphylaxis be observed.

1.8.12 Potential future benefit to patients

The primary objective of this initial study of SLN360 is to determine safety and tolerability in subjects. However, the data generated will provide valuable detailed information regarding the disposition and biological effect of SLN360 when dosed to humans with Lp(a) mediated CVD.

1.8.13 Risk-benefit summary

In conclusion, there is a high unmet medical need for additional therapies for the treatment of Lp(a)-mediated disease. Currently, no therapeutic option is available for the effective, specific reduction of Lp(a), leaving a potent risk factor for a number of manifestations of CVD unaddressed by existing treatments. In the case of AS, currently the only treatment option is surgical or transcatheter aortic valve replacement for patients with severe symptomatic disease, which carries a substantial burden of morbidity and mortality and may not be safe for older, frail patients. SLN360 has displayed an excellent non-clinical safety profile, with no adverse effects in the presence of the expected pharmacodynamic response (see Sections 1.2, 1.3, 1.4, 1.5, 1.6), and is anticipated to have no off-target effects. The Sponsor proposes to initially evaluate the effects of SLN360 in patient who are free of overt CVD or at earlier stages of disease prior to opening the development to individuals with more severe disease later in development.

In summary, the Sponsor believes that the risk-benefit balance for the use of SLN360 is favorable and may represent a significant benefit for the treatment of Lp(a)-mediated conditions.

2 Objectives

The initial part of the study will comprise a SAD part in subjects with elevated Lp(a). The second part of the study will comprise an MD part in subjects with elevated Lp(a). The MD part will begin after a safe and tolerable dose has been established in the SAD part of the study.

The primary objective is:

i. To determine the safety and tolerability of single or multiple doses SLN360 in subjects with elevated Lp(a) levels.

The secondary objectives include assessment of the following:

i. PD effects of single and multiple doses of SLN360 on Lp(a).
ii. PK of SLN360 after a single and multiple dose administration.
iii. Extent and duration of reduction in Lp(a) following single and multiple doses of SLN360.
iv. Impact of dose schedule of SLN360 on extent and duration of reduction in Lp(a).

The exploratory objectives include assessment of the following:

i. Impact of single and multiple doses of SLN360 on lipid profile including apoB, OxPLs, inflammatory markers, and plasminogen.

3 Investigational plan

3.1 OVERALL STUDY DESIGN AND PLAN

This is a phase 1, multicentre, randomised, double-blind, placebo controlled, SAD and MD study to assess the preliminary safety, tolerability, PD and PK of SLN360 administered subcutaneously to subjects with elevated Lp(a).

Sentinel dosing will be employed for each cohort in the SAD: the first 2 subjects in each cohort will be randomised for 1 subject to receive active SLN360 and 1 subject to receive placebo. These two subjects will be dosed a minimum of 24 hours in advance of the rest of the subjects in the cohort.

For each cohort, safety and, where available, PK data will be reviewed and assessed by the SRC before recommending progression to the to the next dose escalation. The study design is summarized in *Figure 1*.

3.2 SAD PART

Up to 5 cohorts, each consisting of 8 subjects (6 active: 2 placebo) with elevated Lp(a) levels will be dosed at the appropriate dose level of SLN360 or placebo administered subcutaneously on Day 1. Subjects will be admitted as inpatients for dosing and for at least 24 hours of post-dose monitoring and assessment. The PD effects of SLN360 will be evaluated by measuring plasma Lp(a) levels as the most proximal measurable marker of target engagement. Effects on a broader lipid profile, including high density lipoprotein (HDL)-cholesterol, LDL-cholesterol and total cholesterol, triglyceride and apoB will also be measured. PK parameters will also be assessed at several timepoints for up to 36 hours after dosing. The SRC may recommend increasing the duration of follow-up beyond the currently planned 150 days, up to a maximum of 365 days. During a planned review, the SRC recommended extension of follow-up for cohorts 3 and 4 to 365 days each. This is now reflected in the Schedule of Assessments (Appendix 5: Schedule of Assessments).

3.3 MD PART

Up to 3 cohorts, each consisting of 12 subjects (9 active: 3 placebo) with elevated Lp(a) levels will be treated with doses and at dose frequencies of SLN360 informed by data from the SAD part. Subjects will be admitted as inpatients for dosing and at least 24 hours of post-dose monitoring and assessment. Subjects will be followed for up to 201 days (duration informed by data from the SAD part) from the first dose to understand the magnitude and durability of the Lp(a) response to multiple dose administration of SLN360. As for the SAD cohorts, the PD effect of SLN360 will be evaluated by measuring plasma levels of Lp(a) and a range of other lipid fractions (LDL-cholesterol, HDL-cholesterol, total cholesterol, triglyceride, and apoB). PK parameters will also be assessed at several timepoints after dosing. The final dose levels and dosing frequency of the MD cohorts will be

dependent on safety, tolerability, PD and PK findings from the SAD part of the study. The SRC may recommend increasing the duration of follow-up beyond the currently planned 201 days up to a maximum of 365 days.

3.4 DOSE ESCALATION DECISIONS

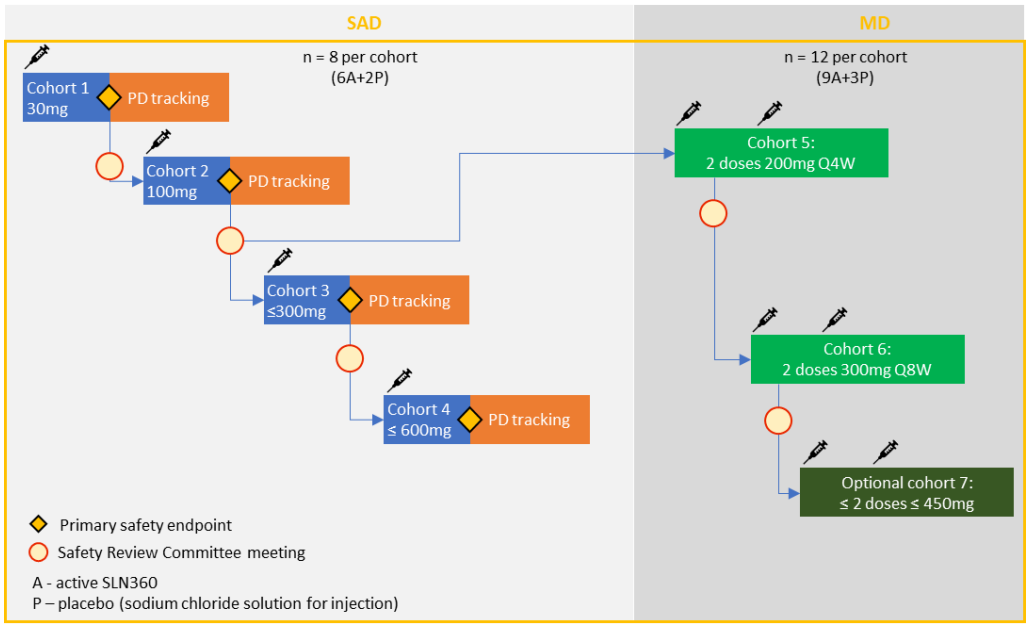
In the SAD part, laboratory and safety data will be collected for up to 7 days after dosing in each cohort. These data will be assessed by a SRC who will make a recommendation to the Sponsor and academic leadership of the study before a decision is made to initiate the next cohort at an escalated dose.

To implement dose escalation decisions, the available toxicity information (i.e. AEs, ISRs, electrocardiograms (ECGs) and all laboratory abnormalities regardless of dose-limiting toxicity [DLT] assessment) will be evaluated by the SRC. Drug administration at the next higher dose cohort may not proceed until the Investigator receives written confirmation from the Sponsor indicating that the results of the previous dose cohort were evaluated and that it is permissible to proceed to the next higher dose cohort.

The SRC may identify an additional or intermediate dose to be evaluated after data review.

The decision to proceed to the MD part and the selected dose recommended by the SRC, will be based on an evaluation of all relevant data available from dose cohorts evaluated in the SAD part of the study, including safety information and lab tests. The final dose levels and dosing frequency for MD cohorts will be dependent on safety, tolerability, PD and PK findings from the SAD part. Please see Section 3.7 for details of dose selection in the SAD and MD parts.

Figure 1: SLN360-001 Study Design Overview



Note: This is an illustrative schematic only. The actual timings of dose escalation and SRC meetings may differ, as described in the protocol and in the SRC charter.

3.5 SAFETY REVIEW COMMITTEE

The SRC will consist of a panel of subject matter experts who are not participating in the study, as described in the SRC charter. The SRC will conduct the safety and, where available, PK, data review of each cohort and recommend dose escalation within the study to the Sponsor.

Safety data for a minimum of two-thirds of subjects who received SLN360 at a particular dose level will be made available and reviewed by the SRC prior to dose escalation to the next level.

The decision to proceed to the next dose escalation of the study will be made by the Sponsor in discussion with the academic leadership of the study, based upon the recommendation of the SRC.

3.6 STUDY DESIGN AND CHOICE OF CONTROL GROUPS

For the SAD part, a sequential group, ascending dose design has been chosen for safety reasons as SLN360 is in the early stages of clinical development, and it is the first time these doses will be administered to humans. An optional cohort may be added to the SAD part of the study to evaluate an intermediate dose level or repeat a dose cohort to better understand the impact of SLN360 at a particular dose level and its suitability for use in the MD part of the study. As this is a phase 1 first-in-human study, sentinel dosing will be employed for subjects in all SAD cohorts.

A full review of the safety, PD and PK data from the SAD part of the study will be performed by the SRC to confirm the optimal dose level and regimens for the MD part of the study. The dosing interval for the multiple dosing in this study is anticipated to be at least four weeks for a total of 2 doses.

Details of the dosing regimen used for the MD part of the study will be documented in the trial master file.

This study will be a placebo controlled and double-blind design in order to avoid bias in the collection and evaluation of data during study conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

3.7 SELECTION OF DOSES IN THE STUDY

The rationale for dose selection based on data from NHP studies is described above (see Section 1.8.3).

The proposed dose escalation scheme of 30, 100, ≤300, ≤600 mg and an optional cohort up to 900mg is approximately 3-fold or less between each cohort. This increase is sufficient to be able to observe an increase in pharmacological effect above the expected variability of PK and PD measures whilst only cautiously increasing the duration of the PD effect in humans. From a primary pharmacology perspective, the participants are subjects who have a high Lp(a) level so exaggerated primary pharmacology is not expected to occur. The dose escalation scheme proposed in the protocol is based on preclinical data and each escalation will be assessed by the SRC. Markers of liver and kidney toxicity will be carefully reviewed prior to each dose increment as these have been identified as potential specific target organs for toxicity in the non-clinical program. If there are any causes for concern, the SRC can recommend a smaller increment in dose escalation.

A top dose of ≤ 900 mg has been selected, in keeping with approximately 3-fold increases in dose levels between cohorts. This dose is anticipated to be at the top of the dose-response curve pharmacologically and is included to provide comprehensive safety and benefit/risk information for subsequent dose selection purposes. A dose of 900 mg is also potentially the highest dose that can be reasonably administered subcutaneously using the current SLN360 formulation.

The proposed IMP dose levels for the SAD and MD parts of the study are shown in *Figure 1* and *Table 1.*

Table 1 - Dose escalation levels

	Cohort (dose)	Dose level description	Minimum no. of SLN360-treated subjects for SRC assessment
SAD part:	1 (30 mg)	1/10 of expected therapeutic dose	4
	2 (100 mg)	Lower limit of expected therapeutic dose	4
	3 (≤ 300 mg)	Expected therapeutic dose	4
	4 (≤ 600 mg)	Upper limit of expected therapeutic dose	4
	4a (≤ 900 mg)	Optional additional dose	4
MD part:	5 (2x ≤ 200 mg) Q4W	n.a.	6
	6 (2x ≤ 300 mg) Q8W	n.a.	6
	7 (≤ 2x ≤ 450 mg)*	Optional additional dose	6

Note: Dose and dosing interval in the MD part to be confirmed based on SAD findings.
*Optional cohort 7 may be used to evaluate either multiple or single dosing. The relevant Schedule of Assessments will be used depending on whether multiple or single dosing is employed.

For the MD part of the study, the dose level in each cohort will be recommended by the SRC based on the safety, PD and PK data from the SAD part of the study. Each dose of SLN360 administered during this part of the study will not exceed the maximum dose level studied in the SAD part of the study. Two doses will be administered in each cohort in the MD part. The interval between the first and second doses in each MD cohort will be determined on the recommendation of the SRC based on available safety, tolerability, PK and PD data from the SAD part. The second dose will be administered no sooner than 4 weeks after the first dose. The maximum dose level administered in each MD cohort will not be greater than that administered during the SAD part. Details of all doses administered in both parts of the study will be documented in the trial master file.

3.7.1 Dose escalation

In the SAD part, the decision to progress from one dose cohort to the next will be recommended by the SRC. The decision to dose escalate will be made based on 7-day safety and tolerability data for at least two-thirds of the subjects within the cohort receiving SLN360. To implement dose escalation decisions, the available toxicity information (i.e., all AEs, ISRs, ECGs and any laboratory abnormalities regardless of DLT assessment) will be evaluated by the SRC. Drug administration at the next higher dose cohort may not proceed until the Investigator receives written confirmation from the Sponsor indicating that the results of the previous dose cohort were evaluated and that it is permissible to proceed to the next higher dose cohort. Although the SLN360 dose scheme is nominally identified from 30mg up to 900mg with an approximate 3-fold step between doses, the SRC may identify an additional dose or dose regimen to be evaluated after data review. Any such decision to invoke the optional cohort at a dose not currently stated, will not be considered a protocol amendment, subject to the dose not being above the maximal dose identified in the protocol (900 mg).

The recommendation to introduce the MD part of the study will be made by the SRC no sooner than 4 weeks after all subjects within the 100 mg SAD cohort receiving SLN360 have completed 90 days of follow-up. The planned doses and regimens in the MD part are shown in *Table 1*. Dosing at a given dose level in the MD part will not commence until the SRC has recommending dosing at the same or a greater dose level in the SAD part. For example, dosing in the ≤ 300 mg MD cohort will not commence until the SRC has recommended escalation from the ≤ 300 mg SAD cohort to the ≤ 600 mg SAD cohort. Following the first dose administration in the MD part, available safety, tolerability and PK data will be reviewed for each subject in order to assess the subject's suitability for administration of the second dose. The SRC will be advised of the findings of that review process. In addition, the SRC will make a recommendation on whether to dose escalate between cohorts in the MD part based on available 7-day safety and tolerability data following the first dose for at least two-thirds of the subjects within the MD cohort receiving SLN360. The optional cohort in the MD part may be used to evaluate either multiple or single dosing; the relevant Schedule of Assessments will be used depending on whether multiple or single dosing is employed.

3.7.2 Stopping rules

3.7.2.1 Stopping rules for study

The SRC will recommend that the Sponsor temporarily halt or stop the study after consideration of the stopping rules (as defined below), otherwise the study will proceed as planned.

The SRC will recommend that the Sponsor stop the study if any of the following scenarios occur and it is considered likely to be causally related to the study drug from the available data:

i. Any serious adverse reaction (i.e. a serious AE [SAE] considered related to the study drug) in two or more subjects during the study.
ii. Any severe non-serious adverse reactions (i.e. an AE considered related to the study drug) in 3 or more subjects during the study.

For the study to be stopped completely, the 2 SAEs or three severe non-serious AEs must be related to the study drug, be medically similar and create an important safety signal as confirmed by the SRC and recommended to the Sponsor.

3.7.2.2 Stopping rules for dose escalation and cohort dosing

The SRC will recommend that the Sponsor stop dose escalation or dosing in a cohort if any of the following scenarios occur with a reasonable possibility of a causal relationship to SLN360:

Two or more subjects have a confirmed QT interval corrected (using the Fridericia formula) for heart rate (QTcF) >500 msec and/or an increase of >60 msec from baseline on repeated ECGs performed at least 2 minutes apart.

i. Two or more subjects have clinical chemistry evidence of significant liver injury, as defined by ANY 1 of the following:
    a. Confirmed increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >5× upper limit of the normal range (ULN)*;
    b. Confirmed increase in alkaline phosphatase (ALP) to ≥ 2 × ULN, particularly with accompanying elevation in γ-glutamyl transferase, in the absence of known bone pathology cause for the rise in ALP level. In subjects with abnormal baseline ALP, confirmed increases will be considered proportionate to this baseline;
    c. Confirmed increase in ALT or AST to ≥ 3 × ULN and simultaneous increase in serum total bilirubin to >2 × ULN or international normalized ratio (INR) to >1.5, without initial findings of cholestasis and where no other reason is found to explain this combination (e.g. confirmed viral hepatitis, other acute or pre-existing liver disease, or another drug capable of causing the injury).

d. Confirmed ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

*For the liver injury criteria, there will be a careful evaluation of available clinical, laboratory, imaging and other data for alternative causes (e.g. acute viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, hepatobiliary disease, non-alcoholic steatohepatitis, cardiovascular causes and concomitant drug or non-prescription therapy). Isolated hyperbilirubinemia or isolated elevation of γ-glutamyl transferase will not be regarded sufficient to qualify as suspected drug-induced liver injury (DILI), but will be considered on a case-by-case basis with appropriate exclusion of potential contributors.

The stopping criteria will be considered a DLT if experienced by subjects in Cohorts 1 to 4 (and 4a, if used) and occur in the DLT assessment period (up to 7 days). Any subject withdrawn due to DLT will be followed to resolution or the end of the study.

Any moderate non-serious adverse reactions will be reviewed in aggregate to assess the number of subjects in whom they occur and concurrency of more than one in the same subject. Following review of the data, it may be considered appropriate to stop further dosing in a cohort or potentially the study.

3.7.2.3 Subject withdrawal and replacement

If a subject is withdrawn, the Sponsor will be notified. The date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn, every effort will be made to perform all follow-up assessments including the end of study visit, if possible (see Appendix 5: Schedule of Assessments). Other procedures may be performed at the Investigator's (or their designee's) and/or the Sponsor's discretion. If the subject is an inpatient at the center, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

If a subject withdraws from this study for any cause before study treatment starts, the subject should be replaced with a new subject who should be assigned a new subject number.

Once dosed, subjects dropping out before the end of the DLT assessment period in the SAD part of the study for any toxicity reasons will be counted as DLT and not be replaced. However, subjects who drop out or are discontinued before the end of the DLT assessment period in the SAD part of the study, which are not due to a DLT, can be replaced to enable a sufficient sample size per cohort for dose escalation decisions. Any replacement subject will also be reviewed by the SRC to confirm no DLT occurred.

4 Selection of study population

4.1 STUDY POPULATION

The following subject population will be studied:

i. Adult (age ≥18 years) subjects with an elevated Lp(a) level.

All subjects should satisfy all the following criteria at the screening visit.

4.2 INCLUSION CRITERIA

i. Male and female subjects aged 18 years to 70 years.
ii. Body mass index of ≥ 18 kg/m^2 and ≤ 45 kg/m^2.
iii. WOCBP must have a negative serum pregnancy test at screening and a urine negative pregnancy test on Day -1.

iv. All subjects must agree to adhere to appropriate contraception requirements (acceptable methods of contraception are summarized below and described in detail in Section 5.8), as follows:
   a. WOCBP must agree to use 1 highly effective method of contraception, from the beginning of the screening period until 3 months after the last administration of study drug.
   b. Male subjects must use a male condom (with or without spermicide) if sexually active with a female of child-bearing potential from the start of the screening period until 3 months after the last administration of study drug.

v. Male subjects are not allowed to donate sperm and female subjects are not allowed to donate eggs from the beginning of the screening period until 3 months following the last administration of SLN360.

vi. Subjects must provide written informed consent, willing and be able to comply with all study requirements.

vii. Elevated plasma Lp(a) $\geq$ 150 nmol/L.

viii. For the MD part only: confirmed history of stable atherosclerotic cardiovascular disease (including, but not limited to, diagnosis of coronary artery disease with or without previous myocardial infarction, previous coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), ischaemic stroke, clinically important carotid artery stenosis, peripheral arterial disease). 'Stable' is defined as the absence of acute cardiovascular disease events within 6 months of screening (including, but not limited to, acute myocardial infarction, unstable angina, acute stroke, acute limb ischaemia).

4.3 EXCLUSION CRITERIA

The presence of any of the following will exclude a subject from enrolment:

i. Comorbidity:
   a. For the SAD part only: any history of clinically overt cardiovascular disease, defined as acute coronary syndromes, myocardial infarction, stable angina, coronary or other revascularization, ischemic stroke or transient ischemic attack and atherosclerotic peripheral arterial disease.
   b. For the MD part only: recent history of acute cardiovascular disease events within 6 months of screening (including, but not limited to, acute myocardial infarction, unstable angina, acute stroke and acute limb ischemia).
   c. Any uncontrolled or serious disease, or any medical or surgical condition including evidence of unstable cardiovascular disease, that may interfere with participation in the clinical study, significantly interfere with the interpretation of the results and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical study.
   d. Moderate or severe hepatic cirrhosis with Child-Pugh grade B or C, or other current or previous liver disease that may increase the risk of drug-induced liver injury or influence the pharmacology of SLN360.
   e. Active serious mental illness or psychiatric disorder, including but not limited to schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention.
   f. Clinically significant illness within 7 days before the first dose of study drug.
   g. Any conditions which, in the opinion of the Investigator, would make the subject unsuitable for enrolment in the study or could interfere with the subject's participation in, or completion of the study.
   h. Positive nucleic acid test for SARS-CoV-2 (the virus causing Covid-19) during screening.
   i. Positive test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBC), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV).

ii. Biochemical and hematological parameters:
   a. Clinically significant abnormalities in screening blood tests (excluding lipid profile) that are judged to affect the suitability for inclusion, including:
      i. ALT or AST >1.5 × ULN.
      ii. Total bilirubin >ULN, except in previously confirmed cases of Gilbert's syndrome.
      iii. Platelet count < lower limit of the normal range.
      iv. Significant renal impairment before randomisation, defined as estimated glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration equation) <60 mL/min/1.73 m^2.
      v. Haemoglobin A_{1c} greater than 6.5% (47.5mmol/mol) in subjects without diabetes mellitus, or haemoglobin A_{1c} greater than 8.5% (69.4mmol/mol) in subjects with diabetes mellitus and on appropriate diabetes treatment.

iii. Concomitant medication:

Subjects with previous or current use of the following therapies are not eligible for participation:

   a. Medication or therapies significantly affecting Lp(a) level (including but not restricted to PCSK9 inhibitors, prescription dose niacin, fibrates or anti-estrogen therapy), unless on a stable dose or off treatment for ≥ 8 weeks prior to screening and no planned medication or dose adjustment during the study.

b. Statins and/or ezetimibe unless on a stable dose or off treatment for at least 8 weeks prior to screening and no planned medication or dose adjustment during the study.
c. Lipid or lipoprotein apheresis.
d. An investigational agent other than SLN360 within 90 days (or 10 half-lives, whichever is longer) before the first dose of study drug.
e. Oligonucleotide therapy, including antisense oligonucleotides and siRNA, other than SLN360, within 12 months of screening.
f. Current use of hormone replacement therapy unless on a stable regimen or off treatment for at least 8 weeks prior to screening and no planned adjustment to the regimen during the study.
g. Current use of anti-estrogen or estrogen receptor modulator (e.g. tamoxifen).

iv. Alcohol and illegal drugs:
a. History or clinical evidence of alcohol misuse within the 6 months before screening.
b. History or clinical evidence of illegal drug use within the 6 months before screening.

v. Drug intolerance:
a. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
b. History of intolerance to s.c. injections or scarring (e.g. from surgical procedures or burns) in skin areas where s.c. doses may need to be administered.

5 Study treatments

5.1 DESCRIPTION, STORAGE, PACKAGING AND LABELLING

SLN360 is a GalNAc conjugated double stranded fully modified siRNA. SLN360 will be provided as a solution for injection for s.c. use (200 mg/mL [as free acid form], presented as 0.5 mL extractable volume per vial). SLN360 will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificates of Analysis.

SLN360 must be kept in an appropriate, secure, locked area and stored in accordance with the conditions specified on the labels. SLN360 will be stored between 2 °C and 8 °C.

Placebo treatment (commercial sodium chloride injection, 0.9% w/v administered via s.c. injection) will be supplied by the Sponsor (or designee). Placebo will be stored in accordance with the conditions specified on the label. All study drug vials/ampoules are single-use and any unused portion remaining in the vial must be discarded before storing for reconciliation.

5.2 STUDY TREATMENT ADMINISTRATION

Each dose of SLN360 or placebo will be administered as s.c. injection(s) by appropriately qualified clinical study site staff. The injection will be delivered in the abdomen, avoiding areas where the skin is red, bruised, tender, hard or in sites of previous scars. Where other medicinal products are required to be given by s.c. administration, these should preferably be administered at different sites.

Individual injection volume at each injection site will not exceed 1.5 mL, and up to 3 injection sites may be used to achieve the required dose. Please refer to the IMP Handling Manual for further guidance.

Where multiple injections are required in one dosing session, injection sites should ideally be separated by a few centimeters, according to local practice. For subjects in the multiple-dose cohorts, injection sites should be rotated to a different location (i.e. not administered in precisely the same place). Injection sites should be recorded in the eCRF.

In the SAD part of the study subjects will receive the dose on Day 1. In the MD part of the study, subjects are planned to receive a first dose on Day 1 and second dose no earlier than Day 28. In the SAD part of the study, the 4 planned dose levels (cohorts) to be tested are 30, 100, 300, and 600 mg, with an optional fifth cohort to receive up to 900 mg. The SRC may also request an additional/intermediate dose in the SAD part of the study. The dose and inter-dose interval for the MD part of the study will be selected based on the safety, PD and PK data from the SAD part of the study.

5.3 RANDOMISATION

All subjects will be centrally randomised using interactive response technology (IRT). For each cohort, 2 subjects will be randomly assigned to receive placebo and 6 subjects will be randomly assigned to receive active SLN360. For the MD part, 3 subjects will be randomly assigned to receive placebo and 9 subjects will be randomly assigned to receive SLN360 in each cohort.

5.4 BLINDING AND UNBLINDING

The Investigators, subjects and Sponsor will be blinded to study drug, but delegated site staff e.g. the site pharmacist(s) will be unblinded. The Investigator and other site staff involved with the study will remain blinded to the treatment randomization code during the study drug assembly procedure.

The study blind may be broken if, in the opinion of the Investigator, an emergency exists in which knowledge of treatment assignment is essential to subject safety. The Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.4.1 Emergency unblinding procedure

Emergency unblinding is defined as a purposeful action to reveal the actual treatment assignment of the study subject whereby the knowledge of the treatment assignment is essential for the clinical management, safety and/or welfare of a specific subject. The Investigator should discuss with the Medical Monitor before unblinding if at all possible.

The IRT system that is used for subject randomisation also allows unblinding at any time should it be required. The roles of who can unblind are defined in the system and include the Principal Investigator at the site. Should the online tool not be available, a helpdesk with 24 hours/day 7 days/week, 365 days/year availability is also available for unblinding via telephone (please see IRT Reference Guide).

An email notification will be sent out immediately after the unblinding has occurred to the roles defined in the IRT, including the Principal Investigator at the site, the Sponsor, the Drug Safety Officer and Physician, and the Medical Monitor. The notification of unblinding will be filed in the Investigator Site File and includes the following information:

i. Subject number.
ii. Site number.
iii. Study/protocol number.
iv. Date and time of unblinding.

The notification of unblinding will not contain the actual treatment assignment.

5.5 TREATMENT COMPLIANCE

The Investigator's unblinded designee will ensure that each subject receives the appropriate dose of the study drug. Only subjects enrolled in the study may receive study drug and only site staff, as outlined in the site accountability log, may administer study treatment.

5.6 DRUG ACCOUNTABILITY

The appropriate study personnel will maintain a log of all study drugs received, dispensed, destroyed and returned. Drug supplies will be inventoried and accounted for throughout the study. Local site drug destruction is acceptable, provided it is authorized by the Sponsor and a certificate of destruction is made available.

5.7 CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

5.7.1 Permitted concomitant medications and therapies

Other than those therapies listed in Section 5.7.2, the use of any concomitant medication/therapy, including over-the-counter (OTC) medications, deemed necessary for the treatment of the subject is permitted during the study. Any medication used for the management of dyslipidemia (including statins, ezetimibe, colesevelam, and implitapide) must have been at a stable dose for at least 8 weeks prior to screening and expected to remain stable for the duration of the study (in the opinion of the Principal Investigator). Sex hormone replacement therapy for male or female subjects will only be permitted if it has been at a stable dose for at least 8 weeks prior to screening and are expected to remain stable for the duration of the study (in the opinion of the Principal Investigator). Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

Acetaminophen (paracetamol), up to a maximum dose of 2g/day, will be permitted for use as an antipyretic and/or analgesic. Aspirin (up to a maximum dose of 325mg/day) will be permitted for use as an antipyretic and/or analgesic, and for primary or secondary prevention of cardiovascular disease. Oral contraceptives are permitted.

5.7.2 Prohibited concomitant medications and therapies

The following concomitant treatments are not permitted during the study:

i. Initiation of medication or therapies significantly affecting Lp(a) level (including but not restricted to PCSK9 inhibitors, prescription dose niacin, fibrates, and anti-estrogen therapy).
ii. Initiation of statins and/or ezetimibe.
iii. Initiation of lipid or lipoprotein apheresis.
iv. Initiation of oligonucleotide therapy, including antisense oligonucleotides, and siRNA, other than SLN360.
v. Initiation of sex hormone replacement therapy for male or female subjects.
vi. Initiation of anti-estrogen or estrogen receptor modulator (e.g. tamoxifen).

If during the course of the study, a subject needs additional medication, surgery or an investigation that affects participation in the study or otherwise compromises either the subject's safety or the integrity of the data collected, this should be discussed with the Medical Monitor. The subject may be withdrawn from the study, if deemed necessary, and replaced. The subject's treating physicians must be informed of the experimental therapy and the likely effects of SLN360 on Lp(a), other plasma lipid fractions and markers of toxicity.

5.8 CONTRACEPTION

Female participants

Female subjects of child-bearing potential (who are heterosexually active) must agree to use 1 highly effective method of contraception from the start of the screening period until 3 months after the last administration of study drug.

In accordance with the guidance from the Clinical Trial Facilitation and Coordination Group of the European Heads of Medicines Agencies, methods that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods. In line with Clinical Trial Facilitation and Coordination Group guidance, such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, or transdermal formulations).
- Progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, injectable or implantable formulations).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical confirmation of surgical success).
- Complete sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

All women are to be considered of child-bearing potential unless they are permanently sterile or postmenopausal:

Permanent sterility: A woman must only be considered permanently sterile if they have clear medical documentation confirming hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Postmenopausal status: A postmenopausal state is defined as no menses for at least 12 months before the start of the screening period, without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range (as per local laboratory guidelines) should be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

Male participants

Male subjects must use a male condom (with or without spermicide) if sexually active with a female of child-bearing potential from the start of the screening period until 3 months after the last administration of study drug. Female sexual partners of male subjects who are of childbearing potential must use 1 highly effective method of contraception as detailed above. Male subjects should be encouraged to inform their female sexual partners that they are participating in a phase 1 clinical study.

Male subjects who have documented vasectomy with medical confirmation of success are not required to use contraception.

5.9 DIETARY RESTRICTIONS AND MEALS

- Consumption of alcohol will not be permitted from 48 hours prior to, and until 48 hours after each dose administration. Subjects' self-reported alcohol use for these periods during the study will be recorded in the eCRF.
- Subjects must abstain from eating food containing poppy seeds within 24 hours of admission and scheduled follow-up visits.
- During the subject's residential stay, the following schedule is recommended for meals and snacks:

Day/meal	Breakfast	Lunch	Dinner	Snack
D-1	-24H	-20H	-14H	-11H
D1	+1H	+4H	+10H	+13H
D2	+24.5H	+28H	N/A	N/A
Note: Timings are given in hours (H) in relation to the time of dosing (H0), D = Day, N/A = not applicable.				

Note: The recommended schedule does not apply to subjects with health conditions that do not allow eating as per a standardized schedule (e.g. diabetes).

5.10 EXERCISE

Subjects are required to refrain from strenuous exercise for 24 hours before and after each study visit, and will otherwise maintain their normal level of physical activity during this time (i.e. will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6 Study assessments and procedures

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 5: Schedule of Assessments). Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. During the inpatient stay the Investigator will ensure availability of all required site facilities, i.e. immediate access to resuscitation equipment, appropriately qualified clinical staff with skills in resuscitation and dealing with acute emergencies, as well as availability of on-site intensive care.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet eligibility criteria; the study Medical Monitor should be consulted for values that are marginal. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1 SAFETY AND TOLERABILITY ASSESSMENTS

6.1.1 Adverse events

AE definitions, assessment of severity and causality including AE, pregnancy and other special situation reporting are detailed in Appendix 1: Adverse event reporting.

AEs will be elicited from the subject (or, when appropriate, from a caregiver, surrogate, or the subject's legally authorized representative) by the study site staff using a non-leading question such as "How are you feeling today?" or "Have you had any health concerns or changes since your last visit?" AEs will also be determined from assessments, including blood and urine tests and ECGs, detailed in the Schedule of Assessments (Appendix 5: Schedule of Assessments).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE and must follow subjects with AEs until the event has resolved or the condition has stabilized. In the case of unresolved AEs, including clinically relevant abnormal laboratory values or unresolved SAEs at the termination visit which are considered related to the study treatment, these events/abnormalities will be followed until resolution, return to baseline, stabilize or until they become clinically not relevant in the opinion of the Investigator and/or Sponsor.

6.1.2 Injection site reaction assessment

The monitoring of AEs will include special attention paid to potential ISRs. The position of the injection sites should be marked at the time of dosing and site reactions monitored throughout the follow-up period. At timepoints specified in the Schedule of Assessments (Appendix 5: Schedule of

Assessments), inspection of the site of administration and surrounding area will be performed. For the MD part, following the second dose this will also include inspection of injection sites for the first dose, to capture any recall phenomena in the eCRF. Additional evaluations of the injection site may be performed if a reaction is observed at the discretion of the Investigator.

ISRs are to be rated and recorded in two ways simultaneously:

First, individual local ISRs will be rated as defined in *Table 2* (based on Guidance for Industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. FDA 2007).

Table 2 - Injection site reaction grading scale

Local reaction	Grade 1	Grade 2	Grade 3
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever for >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents activity
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness[a]	2.5 - 5 cm	5.1 - 10 cm	>10 cm
Induration/swelling[b]	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	>10 cm or prevents activity

Notes:

a) In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

b) Induration/swelling should be evaluated and graded using the functional scale as well as the reaction measurement.

Second, observation of an ISR, based on any findings on the ISR grading scale, will be reported as an AE with the verbatim term "injection site reaction". For each ISR observed, the AE(s) reported should encompass all the ISR findings according to the most severe sign or symptom observed; reporting of 1 AE per finding (i.e. pain, tenderness, erythema, induration) is not required. Where more than one injection is used to administer a dose, ISRs and their related AEs should be recorded separately for each injection site. Severity of all AEs, including those reflecting ISRs, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5 on a 5-point scale (Grade 1 to 5) and reported in detail on the eCRF

6.1.3 Clinical laboratory evaluations

Blood and urine samples will be collected for central clinical laboratory evaluations (including clinical chemistry, hematology, viral serology, and urinalysis) at the times indicated in the Schedule of Assessments (Appendix 5: Schedule of Assessments). Clinical laboratory evaluations are listed in the Safety Laboratory Parameters Section 9.2. For all female subjects of child-bearing potential, a pregnancy test will be performed at the times indicated in the Schedule of Assessments (Appendix 5: Schedule of Assessments).

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

6.1.4 Vital signs

Vital sign assessments will be conducted after a subject has been resting in a supine position for at least 5 minutes. This includes blood pressure, heart rate, respiration rate, and temperature at the timepoints specified in the Schedule of Assessments (Appendix 5: Schedule of Assessments) and when judged to be clinically appropriate.

6.1.5 Electrocardiogram

12-lead ECGs will be obtained at the times indicated in the Schedule of Assessments (Appendix 5: Schedule of Assessments). Subjects must be in a supine position for 5 minutes prior to the ECG. Heart rate, rhythm, PR interval, RR interval, QRS duration, QT interval, QTcF interval, and any significant abnormalities in ECG will be recorded and reviewed by the Investigator. A cardiologist may be consulted if necessary. ECGs should be repeated in the event an abnormality, as specified by the stopping rules in Section 3.7.2, is detected.

6.1.6 Physical examination

Full or abbreviated physical examinations will be performed at specific timepoints as described below.

Full physical examination: to be performed at the at the timepoints specified in the Schedule of Assessments (Appendix 5: Schedule of Assessments). For full physical examinations, the following will be examined and/or measured by the Investigator or appropriately qualified designee: measurements of height and weight, and examination of the skin, eyes, ears, mouth, lymph nodes, respiratory, cardiovascular, gastrointestinal, neurological and musculoskeletal systems.

Abbreviated physical examination: to be performed at the at the timepoints specified in the Schedule of Assessments (Appendix 5: Schedule of Assessments). For abbreviated physical examinations, the assessment will be focused and guided by symptoms reported by the subject, other physical signs detected, and findings from laboratory assessments. It should be conducted by the Investigator or appropriately qualified designee. The examination may include the skin, lymph nodes, respiratory, cardiovascular, gastrointestinal and musculoskeletal systems, and any ad hoc examinations based on signs and symptoms reported during or prior to the visit.

6.1.7 Weight

Body weight (in underclothes) will be recorded at the times indicated in the Schedule of Assessments (Appendix 5: Schedule of Assessments). Notably, body weight should be measured before each dose.

6.2 PHARMACOKINETIC ASSESSMENTS

Blood samples for determination of the plasma concentration of SLN360 will be collected at the timepoints specified in the Schedule of Assessments (Appendix 5: Schedule of Assessments). Plasma concentrations of SLN360 will be determined using liquid chromatography tandem mass spectrometry.

The acceptable blood time collection windows are as follows:

- 15 and 30 minute samples ± 5 minutes
- 1 and 2 hour samples ± 10 minutes
- 4 and 6 hours samples ± 15 minutes
- 6-24 hours samples ± 30 minutes
- 24-48 hours samples ± 60 minutes
- > 48 hours samples same time of day as preceding dose administration ± 3 hours

The actual times of drug administration will be recorded. Following analysis of PK parameters during the SAD part of the study, the exact timepoints for collection of PK sampling will be confirmed for the MD part of the study.

Alteration of PK collection timepoints for the MD part of the study will not constitute a protocol amendment. If additional blood samples are required for the delineation of PK, the total volume of blood extracted per subject will not exceed 10% of the original planned blood volume.

6.3 PHARMACODYNAMIC ASSESSMENTS

The PD effect of SLN360 will be evaluated by measuring Lp(a) levels as the most proximal measurable marker reflecting target engagement.

Exploratory biomarkers include (see also Appendix 3: PD and PK laboratory parameters)

- ApoB
- OxPL
- Inflammatory markers
- Plasminogen

All biomarkers are to be measured centrally. Blood samples will be collected for biomarker evaluations at the times indicated in Appendix 5: Schedule of Assessments.

7 Sample size and data analysis

7.1 DETERMINATION OF SAMPLE SIZE

Four cohorts of 8 subjects (with each consisting of 6 active: 2 placebo) are planned in the SAD part resulting in 24 subjects being exposed to SLN360 and eight subjects being exposed to placebo (cohorts 1–4). An additional cohort of 8 subjects (6 active: 2 placebo) may be evaluated if recommended by the SRC (optional cohort 4a).

Once dosed, subjects dropping out before the end of the DLT assessment period in cohorts 1–4 (or 4a), for any toxicity reasons, considered as a DLT, will be counted as DLT. Subjects who drop out or who are discontinued before the end of the DLT assessment period in cohorts 1–4 (or 4a), and for reasons which are not due to DLT can be replaced to enable sufficient sample size per cohort for dose-escalation decisions.

Three cohorts of 12 subjects (each consisting of 9 active: 3 placebo) are planned in the MD part resulting in 27 subjects being exposed to SLN360 and 9 subjects being exposed to placebo (cohorts 5–7). An additional optional cohort of 12 subjects (9 active: 3 placebo) may be evaluated if recommended by the SRC (cohort 8). Thus, in the MD part of the study, a total of up to 36 subjects will be exposed to SLN360 in up to 4 cohorts, and a total of up to 12 subjects will be exposed to placebo treatment.

Of the total number of subjects planned for enrolment in the study, including both optional cohorts, up to a maximum of 66 evaluable subjects will be exposed to SLN360, and up to a maximum of 22 evaluable individuals will be exposed to placebo over the course of the study.

7.2 ANALYSIS POPULATIONS

The following analysis populations will be included for this study:

i. Screened population: All subjects who signed an ICF.
ii. Safety population: All subjects who received at least 1 dose of study drug.
iii. Pharmacodynamic population: All subjects who received at least 1 dose of study drug and have evaluable PD data.
iv. Pharmacokinetic population: All subjects who received at least 1 dose of study drug and have evaluable PK data.

7.3 GENERAL CONSIDERATIONS

SAD and MD parts of the study will be reported separately. Formal analysis of the data from the SAD part will commence when all subjects in the SAD part have completed their Day 150 visit, therefore the Sponsor and Contract Research Organisation (CRO) may be unblinded to further follow-up for subjects

in cohorts 3 and 4 depending on the timing of database lock and reporting of the SAD part. Formal analysis of the data from the MD part will commence when all subjects in the MD part have completed their final visit. Optional cohorts in either SAD or MD may be analysed and reported separately, which will be detailed in the Statistical Analysis Plan (SAP), if required.

Subjects assigned to placebo from each cohort will be pooled to create an overall placebo treatment arm. SLN360 treatment arms will be presented separately by dose group.

Descriptive statistics will be used to summarize safety, PD and PK endpoints by treatment group. For categorical variables, summary tabulations of frequency and percentage of subjects within each category will be presented along 95% confidence intervals, where appropriate. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values along 95% confidence intervals, where appropriate, will be presented by treatment group.

The SAP for each part of the study (i.e. SAD and MD) will be written and finalized before the closure of the corresponding part of the study, i.e., database closure and unblinding of the randomisation code. The SAP will provide full details of the analyses, the data displays, and the algorithms to be used for data derivations.

7.4 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summary statistics or frequency counts of demographic and baseline data will be presented by treatment group and overall.

7.5 SUBJECT DISPOSITION

Numbers and percentage of subjects in each population will be tabulated by treatment group and overall. Numbers and percentage of subjects completed, as well as those discontinued with the detail of the reasons for discontinuation, will also be summarized.

7.6 SAFETY ANALYSIS

Safety and tolerability will be evaluated by means of DLTs (SAD cohorts only), AE reports, physical examinations, 12-lead ECGs, vital signs and laboratory safety evaluations. Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

The number and percentage of subjects who experienced at least 1 treatment-emergent adverse event (TEAE), study drug-related TEAE, serious TEAE, study drug-related serious TEAE, TEAE leading to study discontinuation, TEAE leading to discontinuation of study and TEAE leading to death will be summarized by treatment group. Summaries will be presented overall and by system organ class, and preferred term using the Medical Dictionary for Regulatory Activities dictionary.

Descriptive statistics of vital signs, 12-lead ECGs, and safety laboratory evaluations at each visit will be presented by treatment group. Pertinent physical examination findings will be listed.

7.7 PHARMACODYNAMIC ANALYSIS

Biomarker data will be listed and summarized using descriptive statistics.

7.8 PHARMACOKINETIC ANALYSIS

Non-compartmental PK analysis will be performed on individual plasma concentration data, using commercial software. The following PK parameters will be determined from the plasma concentrations of SLN360 after single and multiple doses:

i. Area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$)
ii. AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$)
iii. Maximum observed plasma concentration (C_{max})
iv. Time of the maximum observed plasma concentration (T_{max})
v. Apparent plasma terminal elimination half-life ($t_{1/2}$)
vi. Apparent total plasma clearance (CL/F)
vii. Apparent volume of distribution (V_z/F)

Plasma concentrations of SLN360 and PK parameters will be listed and summarized using descriptive statistics. Individual and mean SLN360 concentration-time profiles will also be presented graphically.

7.9 INTERIM DATA REVIEW

There will not be a formal interim data analysis. The SRC will review data on an ongoing basis for each cohort in order to make recommendations to escalate to the next dose, recommend MD dose groups, and evaluate ongoing safety of the study subjects.

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9 Appendices

9.1 APPENDIX 1: ADVERSE EVENT REPORTING

9.1.1 Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history electronic case report form (eCRF). Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the adverse event (AE) eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs.

Wherever possible, a specific disease or syndrome rather than individual associated signs, symptoms or abnormal assessments or laboratory findings should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF.

Of note, surgical procedures that were planned prior to enrolment in the study are not considered AEs if the conditions were known before study inclusion. The medical condition(s) necessitating the surgical procedure should be reported in the subject's medical history.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subjects provide informed consent until the last follow-up visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the AE worsens over time, then increases in intensity should be recorded as separate AEs (with distinct onset dates).

9.1.2 Assessment of severity

Intensity of all AEs will be graded according to the NCI-CTCAE version 5 on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF. Adverse events not listed on the NCI-CTCAE should be graded as follows:

- **Grade 1** = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** = Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- **Grade 3** = Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.
- **Grade 4** = Life-threatening consequences; urgent intervention indicated.
- **Grade 5** = Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedbound.

9.1.3 Relationship to study treatment

The Investigator (or appropriately qualified designee) will make a determination of the relationship of the AE to the study drug using all available data (including detailed history taking, comprehensive clinical and laboratory/imaging assessment as appropriate), taking into account good clinical and scientific judgment and categorize as follows:

9.1.3.1 Related to study treatment

A 'reasonable possibility' of a relationship between an AE to the study treatment is considered if:

- It follows a reasonable temporal sequence from administration of the drug; and
- It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subjects; or it follows a known pattern of response to the test drug.

9.1.3.2 Not related to study drug

'No reasonable possibility' of a relationship between an AE to the study treatment is considered if:

- It is clearly related to extraneous causes;
- It does not follow a reasonable temporal sequence from administration of the test drug;
- It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subjects;
- It does not follow a known pattern of response to the test drug;
- It does not reappear or worsen when the drug is re-administered.

9.1.4 Structured causality assessment for suspected drug-induced liver injury

In the specific case of causality assessment for possible DILI, decision making is based on compatible clinical course, typical changes in hepatic biochemistry and careful, systematic exclusion of all other reasonable causes, e.g. viral hepatitis (including consideration of cytomegalovirus and Epstein-Barr virus), non-alcoholic or alcoholic fatty liver disease, autoimmune hepatitis, hypotension, heart failure, sepsis, biliary tract obstruction including gallstone disease, portal vein thrombosis, metabolic or hereditary liver diseases (e.g. Wilson's disease), and other hepatotoxic drugs.

Comprehensive causality assessment for possible DILI should utilize expert opinion with formal hepatology or gastroenterology expertise as much as possible, particularly in any severe cases, ideally blinded to treatment assignment in line with published recommendations.

In all cases, structured causality assessment should consider: history and concomitant diseases; temporal relationship with study drug, including latency to time from first drug exposure to qualifying laboratory tests or compatible symptoms (e.g. increasing fatigue, anorexia, nausea, vomiting, right upper quadrant pain); pattern of injury (hepatocellular, cholestatic, or mixed) based on the first set of laboratory tests which meet the threshold for possible DILI and using the R value; injury severity, including peak values and assessment of hepatic synthetic function (prothrombin time /international normalized ratio and albumin); washout data – resolution and time taken to reach reduction in serum enzymes to >50% peak and to return to baseline; exclusion of other potential causes of liver injury with appropriate diagnostic evaluation (e.g. viral hepatitis serology, autoimmune hepatitis serology, imaging and histology, if available and clinical outcome.

9.1.5 Follow-up of adverse events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is related to the study drug or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related to the study drug or study procedures at the follow-up visit can be closed out as ongoing at the Investigator's and Sponsor's discretion.

9.1.6 Adverse drug reactions

All noxious and unintended responses to the study drug (i.e. where a causal relationship between an study drug and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions (ADRs).

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP).

9.1.7 Serious adverse events

A SAE is defined as any untoward medical occurrence that at any dose either:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions);
- Results in a congenital anomaly/birth defect; or
- Results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All SAEs, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be related to the study treatment, will be reported to the Sponsor.

9.1.8 Definitions

9.1.8.1 'Life-threatening'

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (i.e. does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

9.1.8.2 'Hospitalisation'

Adverse events requiring hospitalisation or prolongation of hospitalisation should be considered serious. In the absence of an AE, the participating Investigator should not report hospitalisation or prolongation of hospitalisation. In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.

In the following situations, hospitalisation would not qualify as serious:

- Hospitalisation or prolongation of hospitalisation is needed for a procedure required by the protocol;
- Hospitalisation or prolongation of hospitalisation is part of a routine procedure followed by the study center. This should be recorded in the study file;
- Hospitalisation for survey visits or annual physicals fall in the same category;
- Hospitalisation or prolongation of hospitalisation is required for an elective intervention of a pre-existing condition that did not worsen from randomisation; or
- Hospitalisation for social reasons/circumstances.

9.1.9 Adverse events of special interest

An adverse event of special interest (AESI), whether serious or non-serious, is one of scientific and medical concern specific to the Sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the Investigator to the Sponsor. Such an event might warrant further investigation to characterize and understand it. AESIs will include events noted in prior studies.

In addition to SAEs, the following AEs will be reported to the Sponsor within 24 hours even if the nature of the AE is not deemed serious:

- AEs that potentially meet dose-limiting toxicity criteria.
- Injection site reactions will be considered as AEs of special interest in the final analysis. Mild and moderate AEs as defined in Section 9.1.2 of the protocol do not require 24 hour reporting.

9.1.10 Reporting serious adverse events

Initial Reports

All SAEs occurring from the time of informed consent until the final follow-up visit must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the investigator considers related to study must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

The CRO Drug Safety Specialist will forward SAE queries requesting incomplete or missing information directly to the Investigator. It is the Investigator's responsibility to be diligent in providing this information back to the CRO Drug Safety Specialist as soon as it is available.

9.1.11 Pregnancy Reporting

WOCBP must have a negative pregnancy test at screening. Following administration of study drug, any known cases of pregnancy in female subjects will be reported until 3 months after study completion for female subjects and until 3 months after study completion for male subjects. If a subject becomes pregnant during the study or within the safety follow up period defined in the protocol, the investigator is to stop dosing with study drug(s) immediately and the subject should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the investigator/site the Exposure In Utero (EIU) form for completion. The investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow up period defined in the protocol, the investigator should notify Medpace Clinical Safety as described above. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The Investigator will arrange counselling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the follow-up EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

9.1.12 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error and reports of adverse reactions associated with product complaints.

- Overdose: refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied.
  In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the investigator has reason to suspect that the subject has taken additional dose(s).
- Misuse: refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- Abuse: is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Medication Error: Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product by a healthcare professional, patient or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of subjects missing doses of investigational product are not considered reportable as medication error.
- Product Complaint: is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome should be provided, when available.

Safety Contact Information:
Medpace Clinical Safety

Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, dial "3" **or** +1-513-579-9911, dial "3"
Facsimile: +1-866-336-5320 **or** +1-1-513-570-5196
E-mail: medpace-safetynotification@medpace.com

Medpace SAE hotline – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: medpace-safetynotification@medpace.com

9.1.13 Expedited Reporting

The Sponsor/designee will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than seven days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional eight days.

All other SUSARs will be reported to the applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all investigators as required per local regulation.

The requirements above refer to the requirements relating to the investigational medicinal product.

9.2 APPENDIX 2: SAFETY LABORATORY PARAMETERS

All parameters are to be measured centrally. Local laboratory testing may be undertaken at the Investigator's discretion in order to ensure subjects' safety.

Clinical Chemistry	Hematology	Urinalysis	Viral serology
Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase γ-glutamyl transferase Direct bilirubin Indirect bilirubin Total bilirubin Blood urea nitrogen Creatinine Urea Estimated glomerular filtration rate (CKD-EPI) Sodium Potassium Calcium, phosphate and corrected calcium Albumin Glucose[a] High-sensitivity C-reactive protein Human chorionic gonadotropin (hCG)[d] Thyroid function tests Follicle stimulating hormone	Haemoglobin Mean corpuscular volume Haematocrit Red blood cell count Platelet count White blood cell count (total and %) – with differential if abnormal Eosinophil count and % Haemoglobin A_{1c}[b] **Coagulation profile:** Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalized ratio (INR) Fibrinogen	Glucose Protein Occult blood Urobilinogen pH Specific gravity Ketones Urinary albumin/ creatinine ratio Microscopic examination[c] hCG[d]	Hepatitis B: hepatitis B surface antigen; hepatitis B core antibody Hepatitis C antibody HIV screen (HIV 1 and 2)

Abbreviations: aPTT = activated partial thromboplastin time; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; hCG = Human chorionic gonadotropin; HIV = human immunodeficiency virus

Notes:

a) Blood glucose measured predose on each dosing day. Fasting status should be recorded with this measurement.
b) To be measured at screening only.
c) Urine microscopic examination of urine only required if clinically indicated.
d) Woman of child-bearing potential only. Serum hCG at screening; urine hCG thereafter.

Planned blood volumes

Study part	Maximum blood volume
SAD	Up to 370 ml of blood can can be collected for each subject
MD	Up to 630 ml blood can can be collected for each subject

9.3 APPENDIX 3: PD AND PK LABORATORY PARAMETERS

All parameters are to be measured centrally.

PD biomarkers: serum lipids and lipoproteins	PD biomarkers: inflammation and coagulation markers	PK
Lipoprotein(a)* Apolipoprotein B LDL-cholesterol HDL-cholesterol Total cholesterol Triglycerides Oxidized phospholipids	C-reactive protein Interleukin-6 Plasminogen	SLN360 plasma concentration

Note: *Lp(a) should be measured using a molar assay.

9.4 APPENDIX 4: REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

9.4.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (such as recruitment materials, subject information sheets, and other subject facing documents, etc.) must be submitted to an IRB or IEC by the Investigator and reviewed and approved by the IEC before the study is initiated.

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed.

Amendments that are classed as substantial amendments, likely to affect the safety of the subjects or the conduct of the study, must be submitted to the appropriate regulatory authorities and the IRB/IECs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

9.4.2 Finances and insurance

Financing and insurance will be addressed in separate documents.

9.4.3 Informed consent

It is the responsibility of the Investigator to give each subject (or the subject's acceptable representative), prior to participation in the study, full and adequate verbal and written information regarding the objectives and procedures of the study, and the possible risks involved. The subjects must be informed about their rights to withdraw from the study at any time.

Furthermore, it is the responsibility of the Investigator, or a person designated by the Investigator, to obtain informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the study. The Investigator will retain the original of each subject's signed ICF.

The informed consent forms will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent forms used in the study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use.

Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC or study site, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subjects' records.

9.4.4 Subject data protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by the Sponsor or CRO auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.4.5 Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. Authorized Sponsor personnel and regulatory officials will be allowed access to such information.

9.4.6 Data quality assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. See Appendix 9.6 for monitoring arrangements in the event of disruption caused by extenuating circumstances (e.g. infectious disease pandemic).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.4.7 Investigator documentation responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant EDC system on an eCRF in a timely fashion.

All data generated from external sources (e.g. laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

9.4.8 Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement. Unless otherwise specified in the clinical study agreement, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

9.5 APPENDIX 5: SCHEDULE OF ASSESSMENTS

9.5.1 Schedule of Assessments – SAD part

		Treatment period (Days)													
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**7**	**14**	**30 ±3**	**45 ±3**	**60 ±3**	**90 ±5**	**150 ±5**	***210 ±5**	***270 ±5**	***330 ±5**	***EoS 365±7**	**Notes**
Inpatient/overnight stay			●												Inpatient stay from dosing until 24 hours after dosing. See Section 5.9 for meal schedule for overnight stays.
Informed consent	●														
Eligibility criteria review	●	●													Recheck clinical status before first dose.
SARS-CoV-2 testing	(●)														See Appendix 6
Viral serology	●														
Randomisation/IRT		●	(●)												IRT randomization at D-1 or D1
Study drug dosing			●												
Demography	●														
Medical history	●														Includes alcohol and illegal drug use history.
Current medical conditions	●														
Previous/concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Full physical examination (including height and weight)	●	●												●	Height measured at screening only. BMI calculated from measured height and weight.
Abbreviated physical examination			●	●	●	●		●	●						
Vital signs	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 9.5.5 for dosing day schedule. Single assessment at all other visits.
Safety blood and urine markers	●	●	●	●	●	●	●	●	●	●				●	See Section 9.5.5 for dosing day schedule. Single sample at all other visits.
PD blood biomarkers	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 9.5.5 for dosing day schedule. Single sample at all other visits.
Pharmacokinetic blood samples			●	●											See Section 9.5.5 for dosing day schedule. Single sample at all other visits.
Pregnancy test	●	●				●		●	●	●	●	●	●	●	Women of child-bearing potential only. Serum hCG at screening; urine pregnancy test thereafter.
12-lead ECG	●		●	●	●	●		●	●	●				●	See Section 9.5.5 for dosing day schedule. Single ECG at all other visits. ECGs should be repeated in the event an abnormality, as specified by the stopping rules in Section 3.7.2, is detected.

		Treatment period (Days)													
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**7**	**14**	**30 ±3**	**45 ±3**	**60 ±3**	**90 ±5**	**150 ±5**	***210 ±5**	***270 ±5**	***330 ±5**	***EoS 365±7**	**Notes**
AE recording	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Injection site reaction assessment			●	●											See Section 9.5.5 for dosing day schedule. Single assessment at all other visits.

Notes: *Visits beyond Day 150 apply only to subjects in SAD cohorts 3 and 4. Subjects in other SAD cohorts should complete their EoS visit on Day 150, with the assessments as described in the EoS for Day 365 in the Schedule of Assessments.

Abbreviations: AE = adverse event ; BMI = Body Mass Index; ECG = electrocardiogram; EoS = end of study visit; hCG = human chorionic gonadotropin; IRT = interactive response technology; PD = pharmacodynamic; SAD = single ascending dose; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

9.5.2 Schedule of Assessments – MD part (Cohort 5 ± optional cohort 7)

Schedule of Assessments – MD part (Cohort 5 ± optional cohort 7)																				Notes
Procedure	**Treatment period (Days)**																			
	Screening*	**-1**	**1**	**2**	**3**	**7**	**14**	**29**	**30 ±3**	**31**	**32**	**36**	**43**	**60 ±3**	**90 ±5**	**120 ±5**	**150 ±5**	**180 ±5**	**EoS 201±7**	
Inpatient/overnight stay			●						●											See Section 5.9 for meal schedule for overnight stays.
Informed consent	●																			
SARS-CoV-2 testing	(●)																			See Appendix 6
Demography	●																			
Medical history	●																			Includes alcohol and illegal drug use history.
Current medical conditions	●																			
Vital signs	●	●	●			●	●	●	●			●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single assessment at all other visits.
Pregnancy test	●	●							●					●	●	●	●	●	●	Women of child-bearing potential only. Serum hCG at screening, urine test thereafter.
Full physical examination (including height and weight)	●	●							●										●	Height measured at screening only. BMI calculated from measured height and weight.
Abbreviated physical examination			●			●	●	●				●	●	●	●	●	●	●		
Safety blood and urine markers	●	●	●		●	●	●	●	●		●	●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single sample at all other visits.
Viral serology	●																			
PD blood biomarkers	●	●	●			●	●	●	●			●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single sample at all other visits.
12-lead ECG	●		●			●	●		●			●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single ECG at all other visits. ECGs should be repeated in the event an abnormality, as specified by the stopping rules in Section 3.7.2, is detected.
Eligibility criteria review	●	●																		Recheck clinical status before dosing.
Randomisation /IRT		●	(●)																	IRT randomization at D-1 or D1
Study drug dosing			●						●											
Pharmacokinetic blood samples			●	●	●	●	●		●	●	●	●	●	●	●					See Section 9.5.6 for dosing day schedule. Single sample at all other visits.

Schedule of Assessments – MD part (Cohort 5 ± optional cohort 7)																			**Notes**
Procedure	**Treatment period (Days)**																		
	Screening*	**-1**	**1**	**2**	**3**	**7**	**14**	**29**	**30 ±3**	**31**	**32**	**36**	**43**	**60 ±3**	**90 ±5**	**120 ±5**	**150 ±5**	**180 ±5**	**EoS 201±7**	
Injection site reaction assessment			●	●	●	●	●		●	●	●	●	●	●						See Section 9.5.6 for dosing day schedule. Single assessment at all other visits
AE recording**	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►	
Concomitant medication recording**	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►	

Notes

*Up to 28 days before Day 1.
**To be constantly recorded from the time informed consent is provided until the last follow-up visit.
N.B. Subjects may stay overnight at the facility at any time at PI discretion (e.g. for logistical reasons due to travel).

Abbreviations

AE = adverse event; BMI = Body Mass Index; ECG = electrocardiogram; EoS = end of study visit; hCG = human chorionic gonadotropin; IRT = interactive response technology; MD = multiple dose; PD = pharmacodynamic; PI = principle investigator; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

PK collection timepoints

- Day 2: +36:00 hours (± 60 minutes) post Day 1 dose
- Day 3: +48:00 hours (± 60 minutes) post Day 1 dose
- Day 31: +36:00 hours (± 60 minutes) post Day 30 dose
- Day 32: +48:00 hours (± 60 minutes) post Day 30 dose
- All other visits: at same time of day as preceding dose administration (± 3 hours)

Visit Windows

- Days 30, 60: ± 3 days
- Days 90, 120, 150, 180: ± 5 days
- Day 201: ± 7 days
- **Day 29: 1 day before 2nd dose**
- **Day 31, 32, 36 and 43: 1, 2, 7 and 14 days after 2nd dose, respectively**

9.5.3 Schedule of Assessments – MD part (Cohort 6 ± optional cohort 7)

Schedule of Assessments – MD part (Cohort 6 ± optional cohort 7)																				
Procedure	**Treatment period (Days)**																			**Notes**
	Screening*	**-1**	**1**	**2**	**3**	**7**	**14**	**30 ±3**	**59**	**60 ±3**	**61**	**62**	**66**	**73**	**90 ±5**	**120 ±5**	**150 ±5**	**180 ±5**	**EoS 201 ±7**	
Inpatient/overnight stay			●							●										See Section 5.9 for meal schedule for overnight stays.
Informed consent	●																			
SARS-CoV-2 testing	(●)																			See Appendix 6
Demography	●																			
Medical history	●																			Includes alcohol and illegal drug use history.
Current medical conditions	●																			
Vital signs	●	●	●			●	●	●	●	●			●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single assessment at all other visits.
Pregnancy test	●	●						●		●					●	●	●	●	●	Women of child-bearing potential only. Serum hCG at screening, urine test thereafter.
Full physical examination (including height and weight)	●	●								●									●	Height measured at screening only. BMI calculated from measured height and weight.
Abbreviated physical examination			●			●	●	●	●				●	●	●	●	●	●		
Safety blood and urine markers	●	●	●		●	●	●	●	●	●		●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single sample at all other visits.
Viral serology	●																			
PD blood biomarkers	●	●	●			●	●	●	●	●			●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single sample at all other visits.
12-lead ECG	●		●			●	●	●		●			●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single ECG at all other visits. ECGs should be repeated in the event an abnormality, as specified by the stopping rules in Section 3.7.2, is detected.

Schedule of Assessments – MD part (Cohort 6 ± optional cohort 7)

Procedure	Treatment period (Days)																			Notes
	Screening*	-1	1	2	3	7	14	30 ±3	59	60 ±3	61	62	66	73	90 ±5	120 ±5	150 ±5	180 ±5	EoS 201 ±7	
Eligibility criteria review	●	●																		Recheck clinical status before dosing.
Randomisation /IRT		●	(●)																	IRT randomization at D-1 or D1
Study drug dosing			●							●										
Pharmacokinetic blood samples			●	●	●	●	●	●		●	●	●	●	●	●	●				See Section 9.5.6 for dosing day schedule. Single sample at all other visits.
Injection site reaction assessment			●	●	●	●	●	●		●	●	●	●	●						See Section 9.5.69.5.6 for dosing day schedule. Single assessment at all other visits
AE recording**	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►	
Concomitant medication recording**	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►	

Notes

*Up to 28 days before Day 1.
**To be constantly recorded from the time informed consent is provided until the last follow-up visit.
N.B. Subjects may stay overnight at the facility at any time at PI discretion (e.g. for logistical reasons due to travel).

Abbreviations

AE = adverse event; BMI = Body Mass Index; ECG = electrocardiogram; EoS = end of study visit; hCG = human chorionic gonadotropin; IRT = interactive response technology; MD = multiple dose; PD = pharmacodynamic; PI = principle investigator; PK = pharmacokinetics; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

PK collection timepoints

- Day 2: +36:00 hours (± 60 minutes) post Day 1 dose
- Day 3: +48:00 hours (± 60 minutes) post Day 1 dose
- Day 61: +36:00 hours (± 60 minutes) post Day 60 dose
- Day 62: +48:00 hours (± 60 minutes) post Day 60 dose
- All other visits: at same time of day as preceding dose administration (± 3 hours)

Visit Windows

- Days 30, 60: ± 3 days
- Days 90, 120, 150, 180: ± 5 days
- Day 201: ± 7 days
- **Day 59: 1 day before 2nd dose**
- **Days 61, 62, 66 and 73: 1, 2, 7 and 14 days after 2nd dose, respectively**

9.5.4 Schedule of Assessments – Cohort 7, single dose option

Schedule of Assessments – Cohort 7, single dose option															Notes
Procedure	**Treatment period (Days)**														
	Screening*	**-1**	**1**	**2**	**3**	**7**	**14**	**30 ±3**	**60 ±3**	**90 ±5**	**120 ±5**	**150 ±5**	**180 ±5**	**EoS 201±7**	
Inpatient/overnight stay			●												See Section 5.9 for meal schedule for overnight stays.
Informed consent	●														
SARS-CoV-2 testing	(●)														See Appendix 6
Demography	●														
Medical history	●														Includes alcohol and illegal drug use history.
Current medical conditions	●														
Vital signs	●	●	●			●	●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single assessment at all other visits.
Pregnancy test	●	●						●	●	●	●	●	●	●	Women of child-bearing potential only. Serum hCG at screening, urine test thereafter.
Full physical examination (including height and weight)	●	●												●	Height measured at screening only. BMI calculated from measured height and weight.
Abbreviated physical examination			●			●	●	●	●	●	●	●	●		
Safety blood and urine markers	●	●	●		●	●	●	●	●	●	●	●	●	●	See Section 9.5.6 for dosing day schedule. Single sample at all other visits.
Viral serology	●														
PD blood biomarkers	●	●	●			●	●	●	●	●	●	●	●	●	See Section 9.5.69.5.6 for dosing day schedule. Single sample at all other visits.
12-lead ECG	●		●			●	●	●	●	●	●	●	●	●	See Section 9.5.69.5.6 for dosing day schedule. Single ECG at all other visits. ECGs should be repeated in the event an abnormality, as specified by the stopping rules in Section 3.7.2, is detected.
Eligibility criteria review	●	●													Recheck clinical status before dosing.
Randomisation /IRT		●	(●)												IRT randomization at D-1 or D1
Study drug dosing			●												
Pharmacokinetic blood samples			●	●	●	●	●	●	●	●					See Section 9.5.6 for dosing day schedule. Single sample at all other visits.

Schedule of Assessments – Cohort 7, single dose option															**Notes**
Procedure	**Treatment period (Days)**														
	Screening*	**-1**	**1**	**2**	**3**	**7**	**14**	**30 ±3**	**60 ±3**	**90 ±5**	**120 ±5**	**150 ±5**	**180 ±5**	**EoS 201±7**	
Injection site reaction assessment			●	●	●	●	●								See Section 9.5.69.5.6 for dosing day schedule. Single assessment at all other visits
AE recording**	◄	———	———	———	———	———	———	———	———	———	———	———	———	►	
Concomitant medication recording**	◄	———	———	———	———	———	———	———	———	———	———	———	———	►	

Notes

*Up to 28 days before Day 1.
**To be constantly recorded from the time informed consent is provided until the last follow-up visit.
N.B. Subjects may stay overnight at the facility at any time at PI discretion (e.g. for logistical reasons due to travel).

Abbreviations

AE = adverse event; BMI = Body Mass Index; ECG = electrocardiogram; EoS = end of study visit; hCG = human chorionic gonadotropin; IRT = interactive response technology; MD = multiple dose; PD = pharmacodynamic; PI = principle investigator; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

PK collection timepoints

- Day 2: +36:00 hours (± 60 minutes) post Day 1 dose
- Day 3: +48:00 hours (± 60 minutes) post Day 1 dose
- All other visits: at same time of day as preceding dose administration (± 3 hours)

Visit Windows

- Days 30, 60: ± 3 days
- Days 90, 120, 150, 180: ± 5 days
- Day 201: ± 7 days

9.5.5 SAD part - Focused schedules for biological sample collection and safety assessments on dosing days

Procedure	Time before/after dosing (hh:mm) on dosing days										
	Predose	Dosing	+00:15	+00:30	+01:00	+02:00	+04:00	+06:00	+12:00	+24:00	+30:00 - 36:00*
Safety markers – blood and urine	●							●	●	●	
PD biomarkers – blood	●							●	●	●	
Injection-site reaction assessment	●			●	●	●		●	●	●	
12-lead ECG	●				●			●	●	●	
Vital signs	●				●			●	●	●	
Pharmacokinetics – blood	●		●	●	●	●	●	●	●	●	●
Physical examination (as specified in Section 9.5.1)	●										

Notes: *The blood sample collection for PK measurements between 30 and 36 hours post-dose is optional in order to minimise burden on subjects but is to be collected wherever possible.
Following analysis of PK parameters during the SAD part of the study, the exact timepoints for collection of PK sampling will be confirmed for the MD part of the study.

Abbreviations: ECG = electrocardiogram; eCRF = electronic case report form; hh = hour(s); mm = (minutes); MD = multiple dose; PD = pharmacodynamic; PK = pharmacokinetics

9.5.5.1 Time windows for assessments on dosing days

The acceptable windows for all assessments on dosing days are as follows:

- 15 and 30 minute samples ± 5 minutes
- 1 and 2 hour samples ± 10 minutes
- 4 and 6 hours samples ± 15 minutes
- > 6 hours samples ± 30 minutes

The exact timing of each assessment or sample collection should be recorded in the eCRF.

9.5.6 MD part (including Cohort 7, single dose option) - Focused schedules for biological sample collection and safety assessments on dosing days

Procedure	Time before/after dosing (hh:mm) on dosing days											
	Predose	Dosing	+00:15	+00:30	+01:00	+02:00	+04:00	+06:00	+09:00	+12:00	+18:00	+24:00
Safety markers – blood and urine	●							●		●		●
PD biomarkers – blood	●							●		●		●
Injection site reaction assessment	●			●	●	●		●		●		●
12-lead ECG	●				●			●		●		●
Vital signs	●				●			●		●		●
Pharmacokinetics – blood	●		●	●	●	●	●	●	●	●	●	●
Full physical examination (as specified in Sections 9.5.2 and 9.5.3)	●											

Abbreviations: ECG = electrocardiogram; eCRF = electronic case report form; hh = hour(s); mm = (minutes); PD = pharmacodynamic

9.5.6.1 Time windows for assessments on dosing days

The acceptable windows for all assessments on dosing days are as follows:

- 15 and 30 minute samples ± 5 minutes
- 1 and 2 hour samples ± 10 minutes
- 4 and 6 hours samples ± 15 minutes
- 6-24 hours samples ± 30 minutes

The exact timing of each assessment or sample collection should be recorded in the eCRF.

9.6 APPENDIX 6: CONSIDERATIONS FOR CONDUCT OF THE TRIAL DURING COVID-19 PANDEMIC

Given the evolving situation on Covid-19 and potential for emergence of other pandemics, the Sponsor will implement effective mitigation against risks, especially with regard to patient safety and to ensure study integrity is upheld.

Investigators will be responsible for assessing the individual risk to each subject at study enrolment and for the duration of the study. Investigators should continue to follow all local institution policy and procedures, national guidelines and applicable regulatory requirements and guidance. Conduct of the study should not interfere with any public health measures implemented by local, national or Federal or State authorities.

9.6.1 Covid-19 testing

All subjects will be tested for SARS-CoV-2, the virus causing Covid-19, following local procedures using an appropriate validated nucleic acid test. If local procedures for Covid-19 infection prevention and control do not include testing using an appropriate validated test, subjects will be required to undergo testing during screening which will be provided by the Sponsor through a central laboratory or through local testing reimbursed by the Sponsor. Subjects with a positive test will not be eligible for enrolment (see eligibility criteria in Section 4).

Testing will be repeated if subjects either develop symptoms consistent with Covid-19 or report exposure to a known case of Covid-19. Once appropriate and validated tests are available, subjects may be tested for seropositivity to confirm eligibility for the study.

Covid-19 test results will be included in the study database and analyses described in the statistical analysis plan and clinical study report.

9.6.2 Assessment of potential Covid-19-related AEs

The Investigator should consider Covid-19 involvement during assessment of AEs, according to the procedures described in Section 6.1 and Appendix 1: Adverse event reporting. In the event of a suspected AE in which Covid-19 infection is considered likely to be involved, Covid-19 testing may be indicated at the discretion of the study Investigator and Medical Monitor.

9.6.3 Potential impact of Covid-19 on study visits

In the event that a subject is prevented from returning to the site to complete visits, or whose safety could be compromised by attending the site, remote visits will be allowed. The Investigator will be provided with a list of assessments that can be performed by remote collection, following discussion with the Sponsor and Medical Monitor.

9.6.4 Potential impact of Covid-19 on monitoring

Monitoring may be conducted remotely in the event that the visit cannot be conducted on-site due to risk of exposure to the individual or access to the site. The monitor will ensure that subjects' data privacy will be maintained as per local requirements. Additional procedures will be described in the trial master file.

9.6.5 SARS-CoV-2 vaccinations

Silence Therapeutics does not consider it likely that there will be interactions between SLN360 and SARS-CoV-2 vaccination. If a volunteer is able and willing to receive a Covid-19 vaccination, investigators should use their best judgment on the correct timing and administration of SLN360.

SARS-CoV-2 vaccination should receive priority over the SLN360-001 trial. However, to make it easier to distinguish vaccination side effects from SLN360 side effects, Silence Therapeutics'

recommendation is to avoid vaccination (first/subsequent dose) on the same day as SLN360 administration, or within the 7-day DLT period. Where possible, vaccination should also be avoided in the 7 days prior to administration of SLN360.

If a study subject experiences adverse vaccine events, the Investigator(s) should use their judgment as to when or whether to administer subsequent, planned SLN360 drug dose(s). Covid-19 and/or vaccination-related adverse events should be managed and recorded in the same manner as any other adverse event in the study. If Covid-19, or a SARS-CoV-2 vaccination disrupts or causes trial visits/assessments to be missed or delayed, each occurrence must be recorded as a protocol deviation.

Covid vaccinations during the study should be captured in accordance with the below guidance:

- Any vaccinations should be recorded on the prior and concomitant medication page of the CRF and should include all relevant information.
- Each dose should be recorded as a separate entry in the concomitant medication log.

The minimum required information to be captured is:

- Vaccine name (this should be specific and include the generic name, brand name, and batch number where possible)
- Dose and units
- Route
- Date (start date and end date will be the same for a single dose)
- Frequency: other, single dose
- Indication: prophylaxis, Covid-19
- Anatomical site of vaccination to be recorded in free text field for indication to specify details