Study Number: SLN360-002	Compound No.: SLN360
Protocol	Version: 1.0

Title:	A multi-centre, randomised, double-blind, placebo-controlled, Phase 2 study to investigate efficacy, safety and tolerability of SLN360 in participants with elevated lipoprotein(a) at high risk of atherosclerotic cardiovascular disease events.

Effective Date: 09-AUG-2022

EudraCT number: 2022-001876-32

NCT Number: NCT05537571

Short Title: Efficacy, safety and tolerability study of SLN360 in participants with elevated lipoprotein(a) and cardiovascular disease.

Abstract: Despite lipoprotein(a) (Lp[a]) being a prevalent genetic risk factor for onset and progression of several manifestations of cardiovascular disease, there are no approved therapeutics designed to specifically lower Lp(a). SLN360 is a 19-mer double-stranded small interfering RNA targeting *LPA* messenger RNA. *LPA* encodes apolipoprotein(a), the protein specific to the Lp(a) particle, and it is the dominant and rate-limiting element in the synthesis of Lp(a). SLN360 is being developed for reducing the risk of Lp(a)-mediated atherosclerotic cardiovascular disease (ASCVD) by decreasing circulating Lp(a) levels.

This Phase 2 study will evaluate the efficacy, safety and tolerability of SLN360 in participants with elevated Lp(a) at high risk of ASCVD events. Eligible participants will be randomised in a 1:1:2:2:2 ratio into one of five treatment groups and will receive either placebo or SLN360 (300 mg or 450 mg doses) every 16 weeks or 24 weeks. Participation will include a screening period of up to 4 weeks, a treatment period of up to 36 weeks and a follow-up period of up to 24 weeks, reaching the end-of-study visit at Week 60.

The results of the study should further characterise the SLN360 dosing regimen that displays favourable safety and tolerability and has the greatest magnitude and duration of Lp(a) reduction with the lowest dosing frequency. Optimising the combination of magnitude and duration of Lp(a) lowering is likely to confer the greatest clinical benefit with respect to ASCVD risk reduction.

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INVESTIGATOR SIGNATURE PAGE

I agree to conduct this Study in accordance with the requirements of this Clinical Study Protocol and associated study documents and also in accordance with the following:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)
- Local laws and regulations
- Any amendments to these regulations

Investigator Name and Qualifications: _____

_____ _____

Investigator Signature Date

Investigator Affiliation:

Institution: _____

Address: _____

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ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
apo(a)	Apolipoprotein(a)
apoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AUC_{0-last}	Area under the concentration curve to last measurable concentration
CAD	Coronary artery disease
CI	Confidential Interval
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CSR	Clinical Study Report
CVD	Cardiovascular disease
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End-of-study
FIH	First-in-human
GalNAc	N-acetyl-galactosamine
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IRT	Interactive response technology
ISR	Injection site reaction
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mRNA	Messenger RNA
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
QTcF	QT interval corrected using Fridericia's formula
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
Q3M	Dosing every 3 months

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Q4M	Dosing every 4 months
Q6M	Dosing every 6 months
Q16W	Dosing every 16 weeks
Q24W	Dosing every 24 weeks
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
siRNA	Small interfering RNA
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach peak plasma concentration
ULN	Upper limit of the normal range

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PROTOCOL SUMMARY

Rationale

Given the weight of evidence from genetic and observational epidemiology and findings from large outcomes trials of low-density lipoprotein cholesterol (LDL-C)-lowering drugs, pharmacological lowering of lipoprotein(a) (Lp[a]) has the potential to reduce risk of atherosclerotic cardiovascular disease (ASCVD) events. The independence of Lp(a) from established ASCVD risk factors, such as LDL-C, further strengthens the likely benefit of Lp(a)-lowering therapy for individuals whose atherosclerotic disease is driven predominantly by Lp(a). SLN360 is anticipated to offer a clinically important reduction in risk in those who have had a previous ASCVD event and those at high risk of a first event, i.e., with both secondary and primary preventive intent.

Data from the United Kingdom Biobank, a longitudinal study of 500,000 adults, demonstrated a strong prospective association of elevated Lp(a) (equal to or greater than 150 nmol/L) with risk of ASCVD events. Elevated Lp(a) was present in 12.2% of those without and 20.3% of those with pre-existing ASCVD and associated with hazard ratios of 1.50 (95% confidence interval [CI], 1.44–1.56) and 1.16 (95% CI, 1.05–1.27), respectively. Furthermore, in the Multi-Ethnic Study of Atherosclerosis (MESA) (n = 4512) and Dallas Heart Study (n = 2078) cohorts, presence of coronary artery calcification (as determined by computed tomography coronary imaging) in individuals with elevated Lp(a) were strongly predictive of incident ASCVD events (hazard ratio 4.71; 95% CI 3.01 to 7.40 with the highest degree of calcification). Subjects with the lowest level of calcification (score of 1-99) had at least x 2-fold increase in risk. In summary, elevated Lp(a) is a likely risk amplifier both in subjects with a prior history of ASCVD and those without established ASCVD. Lowering of elevated Lp(a) is anticipated to be beneficial to both these groups.

No data are yet available from an outcome trial of a specific Lp(a)-lowering therapy, and the absolute or relative reduction in Lp(a) required to achieve a given reduction in ASCVD risk is unknown. The aim of the proposed Phase 2 study is to characterise the dosing regimen that displays favourable safety and tolerability and has the greatest magnitude and duration of Lp(a) reduction with the lowest dosing frequency in a patient population at high risk of ASCVD events. The weight of observational and genetic epidemiological evidence suggests that optimising the combination of magnitude and duration of Lp(a) lowering is likely to confer the greatest clinical benefit with respect to ASCVD risk reduction.

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Objective(s)

Primary Objective

The primary objective is to evaluate the effect of SLN360 on circulating levels of Lp(a) in participants with elevated Lp(a) at high risk of ASCVD events.

Secondary Objectives

The secondary objectives are to:

- Evaluate safety and tolerability of SLN360 in participants with elevated Lp(a) at high risk of ASCVD events
- Evaluate the effects of SLN360 on LDL-C and apolipoprotein B (apoB) in this population

Exploratory Objective

The exploratory objective is to evaluate the pharmacogenetic effects of germline genetic variation(s) in response to SLN360.

Endpoints

Primary Endpoint

The primary endpoint is the time-averaged change in Lp(a) from baseline to Week 36.

Secondary Endpoints

Safety

The secondary safety endpoint is the safety and tolerability of SLN360, as assessed by:

- Adverse event reports
- Physical examination findings
- Twelve-lead electrocardiograms
- Vital signs
- Laboratory safety evaluations

Pharmacodynamics and Efficacy

The secondary pharmacodynamic and efficacy endpoints are:

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- The change (time-averaged and by visit) in Lp(a) from the Day 1 pre-dose assessment to Week 48
- The change (time-averaged and by visit) in Lp(a) from the Day 1 pre-dose assessment to Week 60
- The change (time-averaged and by visit) in other lipids/lipoproteins, including LDL-C and apoB, from the Day 1 pre-dose assessment to Week 36
- The change (time-averaged and by visit) in other lipids/lipoproteins, including LDL-C and apoB, from the Day 1 pre-dose assessment to Week 48
- The change (time-averaged and by visit) in other lipids/lipoproteins, including LDL-C and apoB, from the Day 1 pre-dose assessment to Week 60

Exploratory Endpoints

The exploratory endpoints are the pharmacogenetic effects of germline genetic variation on response to SLN360, measured by association analysis of genetic variants with markers of SLN360 efficacy, including change in Lp(a).

Study Design

This is a multi-centre, randomised, double-blind, placebo-controlled Phase 2 study to investigate the efficacy, safety and tolerability of SLN360 in participants with elevated Lp(a) at high risk of ASCVD.

The study will be divided into three study periods, comprising screening, treatment and follow-up. An end-of-study visit will be conducted to perform final safety and efficacy assessments.

Eligible participants will receive either placebo or SLN360 and will be randomised in the ratio 1:1:2:2:2 into five treatment groups:

- Group 1: Placebo administered subcutaneously at Weeks 0, 16 and 32 (dosing every 16 weeks [Q16W])
- Group 2: Placebo administered subcutaneously at Weeks 0 and 24 (dosing every 24 weeks [Q24W])
    - This group will be stratified so that half of participants are dosed to match the 300 mg Q24W SLN360 group and half are dosed to match the 450 mg Q24W SLN360 group (with respect to injected volume)
- Group 3: SLN360 300 mg administered subcutaneously at Weeks 0, 16 and 32 (Q16W)
- Group 4: SLN360 300 mg administered subcutaneously at Weeks 0 and 24 (Q24W)
- Group 5: SLN360 450 mg administered subcutaneously at Weeks 0 and 24 (Q24W)

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Placebo

The placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related. The placebo is used since no appropriate active comparator is available; notably, there being no approved pharmacotherapy available that has been shown to yield a clinically meaningful lowering of Lp(a) in people with elevated levels.

Study Population

Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria are met:

1. Male or female
2. Aged 18 to 80 years inclusive at screening
3. Lipoprotein(a) at screening equal to or greater than 125 nmol/L
4. At high risk of ASCVD, i.e., at least one of the following conditions:
    a. Previous myocardial infarction (MI)
    b. Coronary angiographic diagnosis of coronary artery disease with or without previous MI
    c. Computerised tomography/magnetic resonance imaging diagnosis of coronary artery disease with or without previous MI
    d. Previous coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft)
    e. Prior ischeamic stroke as previously confirmed by a documented brain imaging study (e.g. computed tomography or magnetic resonance imaging brain), and considered not to be caused by thromboembolic phenomena associated with atrial fibrillation, valvular heart disease or mural thrombus
    f. Peripheral arterial disease
    g. Existing evidence of coronary artery calcium on computerised tomography (coronary artery calcium score ≥1 AU)
5. A body mass index at screening in the range 18.0 to 32.0 kg/m^2, inclusive
6. Participants must be able to provide valid informed consent and to comply with all study requirements
7. Participants receiving lipid-modifying therapy (including statins, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, ezetimibe) must be on a stable, maximum tolerated regimen, according to the clinical judgement of the Investigator, at screening (i.e., receiving therapy for a minimum of 8 weeks) with no

[redacted]

changes to existing regimens or introduction of new regimens made after screening. For monoclonal antibody PCSK9 inhibitors, a stable dose is defined as at least four doses at a consistent dose level

Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria are met:

1. Cardiovascular disease-related:
    a. Acute cardiovascular event within the 12 weeks before screening (including but not limited to acute MI, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, stroke, acute limb ischaemia, limb revascularisation)
    b. Planned or expected cardiac surgery or coronary or other revascularisation within 12 weeks of screening or planned major non-cardiac surgery during the study period
2. Medical history:
    a. Renal dysfunction with estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 (according to the Chronic Kidney Disease Epidemiology Collaboration equation) at screening
    b. Acute, chronic or historical liver disease, including viral hepatitis (hepatitis A, B or C virus) at screening. Participants with positive hepatitis B virus surface antibody titre reflecting hepatitis B virus immunisation are permitted to participate
    c. Hepatic dysfunction based on liver function markers at screening: aspartate aminotransferase, alanine aminotransferase or total bilirubin >2 × the upper limit of the normal range (ULN)
    d. Established diagnosis of Gilbert syndrome
    e. Inherited or other bleeding disorders
    f. Malignancy (except non-melanoma skin cancers, cervical *in situ* carcinoma, breast ductal carcinoma *in situ*, stage 1 prostate carcinoma, or benign tumours) within the 5 years before screening
    g. Current or previous history of moderate to severe heart failure (New York Heart Association Functional Classification grade III or IV at screening) or last known left ventricular ejection fraction less than 30% at screening
    h. Ventricular tachycardia, atrial fibrillation with rapid ventricular response or supraventricular tachycardia that are not controlled by medications in the 12 weeks before screening
    i. Fasting triglycerides >400 mg/dL (4.5 mmol/L) at screening

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j. Uncontrolled hypertension at screening, defined as an average sitting systolic blood pressure > 160 mmHg or an average diastolic blood pressure >110 mmHg after a minimum of three measurements

k. Type 1 diabetes mellitus or poorly controlled (glycated haemoglobin ≥10% or ≥86 mmol/mol) type 2 diabetes mellitus at screening

l. Known active infection or major haematological, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the Investigator at screening or Day 1

3. Concomitant medication:

a. Currently receiving or <12 weeks at Day 1 since receiving >200 mg/day niacin or niacin derivative drugs (e.g., niceritrol, nicomol)

b. Treatment with lipid/lipoprotein apheresis within the 12 weeks before screening

c. Treatment with a cholesteryl ester transfer protein inhibitor (e.g., anacetrapib, dalcetrapib, evacetrapib, obicetrapib) or lomitapide within the 52 weeks before screening

d. Treatment with aspirin, clopidogrel, ticagrelor or other antiplatelet agent unless prescribed at a low maintenance dose for the purpose of cardiovascular risk reduction (i.e., aspirin up to 325 mg daily, clopidogrel 75 mg daily, ticagrelor 180 mg daily)

e. Participation in another clinical trial including an investigational medicinal product within 12 weeks, or within five half-lives of that investigational medicinal product, before screening

f. Any previous use of approved or experimental small interfering RNA therapy (e.g., inclisiran). NB: use of messenger RNAbased vaccines for infectious diseases is permitted

g. Use of approved or experimental antisense oligonucleotide therapy within the 24 weeks before screening. NB: use of messenger RNA-based vaccines for infectious diseases is permitted

h. Use of experimental Lp(a)-reducing therapy within the 52 weeks before screening

i. Use of herbal or complementary medicines, dietary supplements or vitamins known to substantially influence lipid metabolism or blood lipid or lipoprotein levels (e.g., fish oil, turmeric, red yeast rice) within the 4 weeks before Day 1

4. Alcohol and illegal drugs:

a. History or clinical evidence of alcohol misuse within the 26 weeks before screening

b. History or clinical evidence of recreational drug use within the 26 weeks before screening

[redacted]

5. Other exclusions:
    a. Female participants of childbearing potential with a positive serum pregnancy test assessed at screening or positive urine pregnancy test on Day 1
    b. Female participants of childbearing potential planning to become pregnant or breastfeed during treatment and for an additional 12 weeks after the last dose of study treatment
    c. Female participants of childbearing potential unwilling to use a highly effective method of contraception during treatment and for an additional 12 weeks after the last dose of study treatment
    d. Male participants must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the participant must be using a highly effective contraception method from the time of signing the informed consent form until at least 12 weeks after the last dose of study treatment
    e. Known sensitivity to any of the products to be administered during dosing
    f. Likely to be unavailable to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the participant and Investigator's knowledge
    g. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the Investigator or Sponsor, if consulted, would pose a risk to the participant's safety or interfere with the study evaluation, procedures or completion.

Study Assessments

Study assessments will be performed as detailed in the Time and Events tables in Appendix 15.1 (Groups 1 and 3; Q16W dosing) and Appendix 15.2 (Groups 2, 4 and 5; Q24W dosing).

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1. INTRODUCTION

1.1. Background

Elevated baseline levels of lipoprotein(a) (Lp[a]), a genetically determined low-density lipoprotein-like particle linked to apolipoprotein(a) (apo[a]), have been associated with increased risk of cardiovascular events in epidemiological studies [Emerging Risk Factors Collaboration, 2009] and Mendelian randomisation analyses [Larsson *et al*, 2020]. These studies showed that a genetically determined doubling of Lp(a) plasma levels resulted in a 22% increased risk of myocardial infarction (MI), consistent with a causal relationship between lifelong elevation in Lp(a) levels and MI risk [Kamstrup *et al*, 2009]. The *LPA* gene encodes apo(a), and it genetically determines increased plasma Lp(a) levels and apo(a) isoform size. *LPA* risk alleles (i.e., those determining elevated Lp[a] levels) have been linked with other atherosclerotic adverse outcomes, including ischaemic stroke, peripheral artery disease, abdominal aortic aneurysm, obstructed coronary vessels (and therefore increased coronary atherosclerotic burden) and earlier onset of coronary artery disease (CAD) [Helgadottir *et al*, 2012; Larsson *et al*, 2020]. In addition, elevated Lp(a) and the presence of coronary artery calcification detected on computed tomography imaging identifies individuals at high risk of atherosclerotic cardiovascular disease (ASCVD) events [Mehta *et al*, 2022].

Lipoprotein(a) is the major carrier of oxidised phospholipid in human plasma [Zheng *et al*, 2019]. Oxidised phospholipids are mediators of potent proatherogenic and proinflammatory effects that account for a significant proportion of the cardiovascular risk attributable to Lp(a) [Que *et al*, 2018]. Critically, variants in *LPA* strongly associate with oxidised phospholipid-apolipoprotein B (apoB) concentration [Saleheen *et al*, 2017].

Large-scale population data suggest that low levels of Lp(a) are not detrimental to human health, rather they associate strongly with lower risk of cardiovascular diseases (CVDs) [Emdin *et al*, 2016]. Notably, the complete absence of circulating Lp(a) has no effect on increasing morbidity or mortality [Emdin *et al*, 2016; Lim *et al*, 2014]. Additionally, direct pharmacological reduction of Lp(a) through gene silencing has been evaluated clinically and it did not associate with any safety concerns due to Lp(a) reduction [Tsimikas *et al*, 2015; Viney *et al*, 2016; Tsimikas *et al*, 2020; Koren *et al*, 2022].

SLN360 is a 19-mer double-stranded small interfering RNA (siRNA) targeting *LPA* messenger RNA (mRNA). *LPA* encodes apo(a), the protein specific to the Lp(a) particle, and it is the dominant and rate-limiting element in the synthesis of Lp(a). SLN360 covalently links to a tri-antennary N-acetyl-galactosamine (GalNAc) moiety. The GalNAc residues of SLN360 specifically bind the asialoglycoprotein receptor that is expressed on hepatocytes. Therefore, these modifications ensure that SLN360 is targeted to hepatocytes, as demonstrated by nonclinical tissue distribution studies where SLN360 is found in meaningful concentrations only in the liver (the target organ) and the kidneys

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(the organs of excretion). Following binding and receptor-mediated cellular uptake by endocytosis, *LPA* mRNA is targeted for degradation via RNA interference through 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.

SLN360 is being developed for reducing the risk of Lp(a)-mediated ASCVD by decreasing circulating Lp(a) levels. This study aims to evaluate doses and dosing regimens of SLN360 in participants at high risk of ASCVD events.

1.1.1. Name and Description of the Investigational Product

Silence Therapeutics is developing SLN360 to reduce the risk of major cardiovascular events in adults with elevated Lp(a) and at high risk of a first ASCVD event. SLN360 is a 19-mer double-stranded siRNA oligonucleotide that is chemically stabilised and covalently linked to a tri-antennary GalNAc delivery moiety.

SLN360 will be provided as a solution for injection for subcutaneous use in glass vials. A 2 mL injection vial contains 0.5 mL (extractable volume) of an aqueous sterile solution of SLN360 drug substance with a concentration of 200 mg/mL (as free acid form). The vials are intended for single use. The concentration of 200 mg/mL refers to 200 mg SLN360 drug substance expressed as free anhydrous oligonucleotide (acid form) corrected for duplex purity.

1.1.2. Nonclinical Studies

Full details of the nonclinical development of SLN360 can be found in the Investigator's Brochure (IB).

1.1.2.1. Nonclinical Pharmacology

A range of *in vitro* and *in vivo* studies have been performed to characterise the pharmacodynamic (PD) effects of SLN360.

In vitro, SLN360 potently reduces *LPA* mRNA levels in cynomolgus monkey and human primary hepatocytes.

Adequate *in vivo* delivery and potency of SLN360 was investigated initially in healthy naïve animals. The first studies (DD-0001, DD-0004 and STEPS-0069; see IB) were performed with STS20041L6, which has an identical siRNA sequence and carries the same GalNAc ligand as SLN360; however, SLN360 has a different pattern of 2'-O-Methyl and 2'Fluoro on the sense strand. No difference in the pharmacological potency of the two agents was observed (DD-0001, STEPS-0069 and STEPS-0099). The *in vivo* studies in naïve animals (STEPS-0069 and STEPS-0099) confirmed the intended prolonged reduction in serum Lp(a) levels (greater than 80%) after a single subcutaneous

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injection of 3 mg/kg STS20041L6 and SLN360, with a sustained reduction greater than 50% from baseline observed after 2 months. STS20041L6 and SLN360 were well tolerated, and no adverse clinical effects were observed.

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

The *in vivo* studies in naïve animals confirmed the anticipated PD changes that were expected from specific inhibition of *LPA* mRNA expression.

Safety pharmacology parameters were assessed during the course of the 29-day and 13-week Good Laboratory Practice (GLP) studies. In rats (STEPS-0105), SLN360 did not cause any behavioural or motor reflex changes in the Irwin assessments. In cynomolgus monkeys (STEPS-0106), no test-article related findings for electrocardiogram (ECG), blood pressure or respiration were observed.

1.1.2.2. Nonclinical Pharmacokinetics, Toxicokinetics and Absorption, Distribution, Metabolism and Excretion

Repeat-dose studies have been conducted for SLN360. *LPA* gene expression is restricted to humans, great apes and old-world monkeys. The basis for selecting a non-human primate primarily lies with the expression of the target *LPA* sequence, which is specifically expressed in non-human primates 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.

Extensive nonclinical safety and pharmacokinetic (PK) evaluation data of SLN360 has been accumulated, including studies on *in vitro* metabolism, biodistribution, protein plasma binding, repeat dose toxicity in two animal species (rat & cynomolgus monkey), safety pharmacology, antigenicity and genetic toxicity. Drug-drug interaction studies (cytochrome P450 [CYP] inhibition and induction studies, transporter substrate and inhibition tests) have also been carried out (STEPS-0120, STEPS-0124, STEPS-0125 and STEPS-0126).

Toxicological studies with SLN360 were conducted using exaggerated dosing regimens, which contrasted markedly with the doses projected for clinical therapeutic evaluation. Biodistribution in the rat was affected by liver and renal changes at high doses; however, SLN360 in the liver declined to tissue levels less than or equal to 1% of peak levels 3 weeks after dosing. Therefore, significant tissue accumulation is not expected in clinical trials with less frequent dosing.

In a rat biodistribution study, SLN360 was detected at significant concentrations in the liver and kidney, but it remained limited in other organs (including reproductive organs). This distribution pattern was consistent with the specificity of the GalNAc hepatic delivery system and the main renal route of elimination [Janas *et al*, 2018].

SLN360 plasma protein binding was comparable in rats (96.2% to 97.0%), monkeys (97.5% to 97.9%) and human plasma (94.0% to 96.4%; STEPS-0120). SLN360 was chemically and metabolically stable in rat, monkey and human hepatic post-mitochondrial supernatant fractions (S9) and monkey and human hepatic lysosomes (STEPS-0121 and STEPS-0122). SLN360 impacts CYP enzymes CYP2C8, CYP2C9, CYP2C9, CYP1A2, CYP2B6 and CYP3A4/5 at concentrations considerably higher than concentrations expected following clinical exposure to SLN360; subsequently, the effect of SLN360 on CYP expression is not considered to be of clinical significance. The liver and kidneys are the toxicological target organs identified in the nonclinical safety evaluations of SLN360 and are amenable to routine monitoring in clinical studies. Therefore, the associated risk at pharmacological dose levels of SLN360 is considered minimal.

1.1.2.3. Toxicology

SLN360 was well tolerated in a 29-day rat GLP toxicity study, with no test article-related mortality. In a similar 29-day cynomolgus monkey GLP study, SLN360 was well tolerated, with non-adverse reversible findings in the liver (increased weight with diffuse hepatocyte hypertrophy) and lymph nodes (macrophage vacuolation; STEPS-0106).

Similarly, in an extended 13-week cynomolgus monkey study using 30 mg/kg or 100 mg/kg SLN360, both doses did not elicit any adverse effects; moreover, there were non-adverse reversible liver findings as well as granular macrophages in the lymph nodes of at least one animal. An increased SLN360 dose of 200 mg/kg was also tolerated, but it was also associated with mortality (one animal during the recovery phase), body weight loss, hair loss, impaired menstrual cycling, increased liver enzymes (with correlating hepatocellular hypertrophy, degeneration and single cell necrosis), hepatic sinusoidal pigmented macrophages, granular macrophages in the lymph nodes and slight renal tubular vacuolation (STEPS-0128). This was considered mainly related to a dysmetabolic and diabetic status in concert with cardiomyopathy of an uncertain origin, but a role for SLN360 could not be ruled out. Based on these findings, the no-observed-adverse-effect level of SLN360 was established at 100 mg/kg.

Nonclinical safety evaluations of SLN360 have not revealed any unexpected findings. Supra-pharmacological doses of SLN360 in rat studies have highlighted the potential for liver and kidney pathology. Cynomolgus monkey studies have revealed adaptive changes in the draining lymph nodes and liver. These changes were generally observed with the siRNA drug class of molecules, are independent of the sequence-directed target specificity of siRNA and are reversible effects related to temporary drug accumulation in tissues [Janas *et al*, 2018]. No genotoxicity of SLN360 was observed in any of the *in vitro* (STEPS-0118 and STEPS-0119) or *in vivo* (in STEPS-0105) studies conducted, which is in accordance with other siRNAs of this class [Berman *et al*, 2016].

Overall, the toxicological data obtained thus far are regarded as adequate to support single and repeated intermittent treatment with SLN360. The highest dose of SLN360 to

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be used in the proposed clinical study is 450 mg, which is lower than the highest dose that has been administered to date in an ongoing first-in-human (FIH) study of SLN360 (600 mg) [Nissen *et al*, 2022].

1.1.2.4. Immunogenicity

To assess the potential for anti-drug antibodies against SLN360, SLN360 was coupled to a carrier protein (haemocyanin from *Limulus polyphemus* haemolymph), formulated in adjuvant and injected into rabbits intramuscularly on six separate occasions (1 mg/kg [Dose 1], 0.5 mg/kg [Doses 2 to 5] and 0.25 mg/kg [Dose 6]) over a 16-week period (STEPS-0100). No antibodies specific to SLN360 were generated, suggesting that the risk of anti-drug antibody formation is minimal.

1.1.3. Clinical Studies

One ongoing clinical study of SLN360 has been conducted to date. This FIH study is a Phase 1 randomised, double-blind, placebo-controlled, single ascending dose (SAD) and multiple dose (MD) study to assess preliminary safety, tolerability, PK and PD parameters of SLN360 administered subcutaneously to participants with elevated Lp(a) equal to or greater than 150 nmol/L (APOLLO; ClinicalTrials.gov identifier NCT04606602; EudraCT identifier 2020-002471-35). The SAD part of the study locked in January 2022 and results are published, with the MD part currently planned to be completed in 2023.

The SAD part of the study evaluated subcutaneous placebo (0.9% sodium chloride) and single doses of 30 mg, 100 mg, 300 mg and 600 mg SLN360 in healthy adults with an Lp(a) level equal to or greater than 150 nmol/L at screening. Four cohorts, each consisting of eight participants (two placebo, six active), were dosed with either placebo or SLN360 administered subcutaneously in the abdomen on Day 1 and followed up to Day 150. On the recommendation of the Safety Review Committee, follow-up of Lp(a) levels for participants in the 300 mg and 600 mg cohorts was extended from 150 to 365 days.

1.1.3.1. Demographics

In the SAD part of the APOLLO FIH trial, a total of 32 participants were included. The mean age of the study participants was 49.6 years, with 15 males and 17 females (one female was of childbearing potential). Enrolled participants were Caucasian (62.5%), African American/Black (34.4%) and Asian (3.1%). Although none of the participants had known pre-existing clinically overt CVD, hypertension was present in three (9.4%) participants and diabetes in one (3.1%) participant. Of the 32 participants, 13 (41%) participants were taking statins as concomitant medication (participants were in the placebo, 100 mg, 300 mg and 600 mg treatment groups).

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1.1.3.2. Pharmacokinetics

To assess PK parameters, plasma SLN360 concentration was measured, as well as maximum plasma concentration, time to reach peak plasma concentration (T_{max}) and area under the concentration curve to last measurable concentration (AUC_{0-last}).

SLN360 plasma concentration increased in a dose-dependent manner among the dosing groups. Median T_{max} was 4.0 hours for the 30 mg group and 6.0 hours for the 100 mg, 300 mg and 600 mg groups. The AUC_{0-last} measurements followed a similar increasing trend that depended on dose. Insufficient datapoints were available after T_{max} in the SAD cohorts to reliably estimate the plasma apparent terminal elimination half-life; subsequently, plasma elimination half-life will be evaluated in the MD cohorts after denser PK sampling. The PK parameters obtained in the SAD cohorts are detailed in Table 1.

Table 1 Pharmacokinetic parameters of SLN360 for the single ascending dose cohorts in the first-in-human study of SLN360 (SLN360-001)

PK Parameter	SLN360 Dose Groups (N=24)			
	30 mg (N=6)	100 mg (N=6)	300 mg (N=6)	600 mg (N=6)
C_{max} (ng/mL)	115.8 ± 32.6	265.7 ± 125.5	979.2 ± 386.6	3035.0 ± 1131.4
T_{max} (h)	4.0 (0.5 to 6.3)	6.0 (4.0 to 12.0)	6.0 (6.0 to 12.0)	6.0 (4.0 to 12.1)
AUC_{0-last} (h*ng/mL)	898.0 ± 219.4	3229.8 ± 809.9	13166.1 ± 4295.8	36719.9 ± 9530.9

AUC_{0-last}=area under the concentration curve to the last measurable concentration; C_{max}=maximum plasma concentration; PK=pharmacokinetic; T_{max}=time to reach peak plasma concentration
Note: Measurements of C_{max} and AUC are presented as mean ± standard deviation and T_{max} is presented as median (minimum to maximum).

1.1.3.3. Pharmacology

SLN360 PD was evaluated by measuring serum Lp(a) concentration and the effects of SLN360 on concentrations of other lipids and lipoproteins. The lipid profile included high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides and apoB.

The maximal total and percent changes in Lp(a) following administration of placebo or SLN360 across the four dose groups (30 mg, 100 mg, 300 mg and 600 mg) are presented in Table 2. Reductions in Lp(a) were dose proportional and reached a maximal median (interquartile range) percent change of -98% (-98%, -97%) following administration of 600 mg SLN360. The greatest percent change in Lp(a) level concentration was achieved between 30 days and 60 days after dosing for all treatment groups. Subsequently, concentrations gradually rose, but they had not returned to baseline values 150 days post-dose for the 100 mg, 300 mg and 600 mg treatment groups. Median Lp(a)

[redacted]

[redacted]

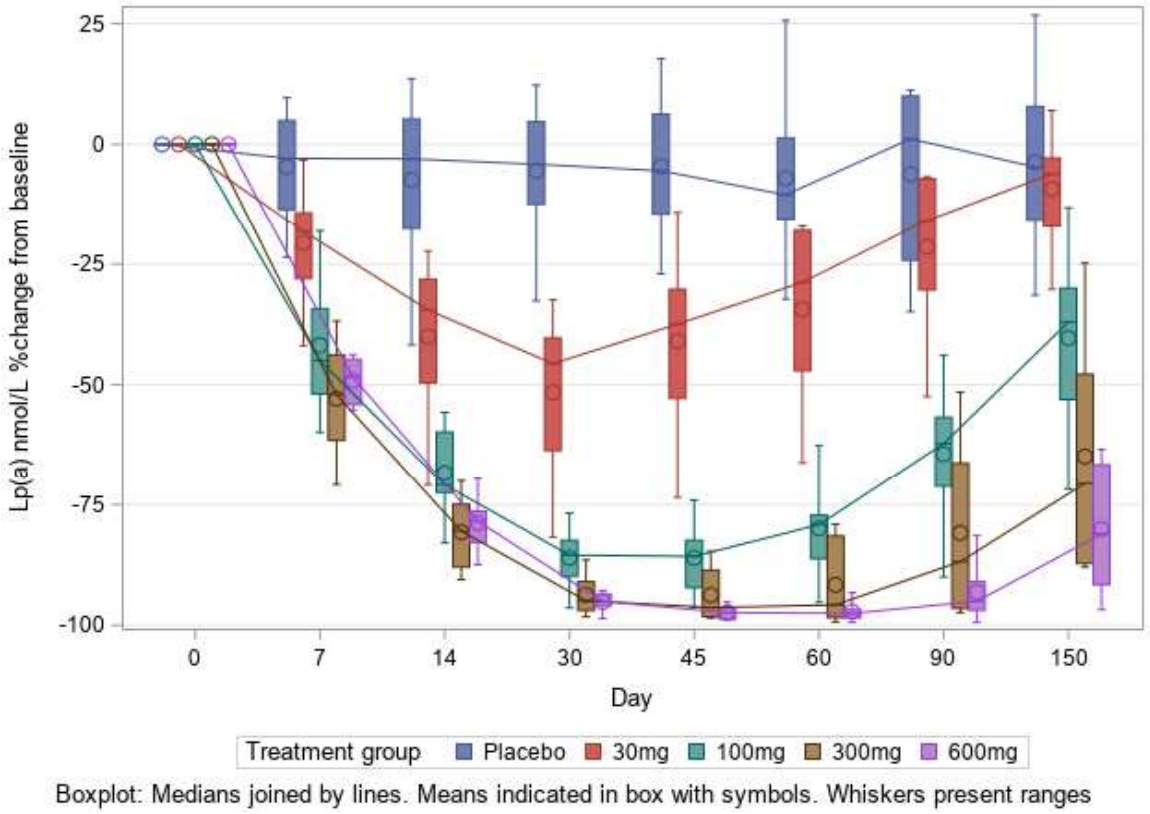
[redacted]

[redacted]

[redacted]

[redacted]

Figure 1 Percent change in lipoprotein(a) concentration from baseline to Day 150 post-dose



Lp(a)=lipoprotein A
Note: ranges presented depict minimum and maximum values.

SLN360 produced a moderate, dose-dependent reduction in apoB-containing lipoproteins (i.e., Lp[a] and LDL, and reflected by total cholesterol). Mean levels were reduced by a maximum of 18% for total cholesterol and 26% for LDL-C, both following administration of the 600 mg dose. Smaller reductions were observed at lower doses. The maximum reduction in the mean level of apoB was 24% at 30 days after the 600 mg dose and 19% at 14 days after the 300 mg dose. The maximal mean percent reduction of oxidised LDL was 20% in the 600 mg dose group at Day 30 and 11% in the 300 mg dose group at Day 90. There was no evidence of an SLN360-mediated effect on triglycerides or high-density lipoprotein cholesterol.

1.1.3.4. Safety

Safety and tolerability were evaluated by dose-limiting toxicities, adverse events (AEs), physical examination, 12-lead ECGs, vital signs and laboratory safety parameters. Injection site AEs potentially meeting the criteria for dose-limiting toxicities were

[redacted]

designated as AEs of special interest. The positions of the injection sites were recorded at the time of dosing and ISRs were monitored intensively for 7 days after dosing and thereafter as AEs, if indicated.

Treatment-emergent AEs (TEAEs) were generally mild and the most commonly reported TEAEs were low-grade injection site events (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0; Grades 1 and 2) and headache (CTCAE Grades 1 to 3, of which a single event was Grade 3 and was ascribed to the effects of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] vaccination), none of which resulted in participant withdrawal. At Day 45, a single participant in the lowest dose group (30 mg) was admitted to hospital for fever and a severe headache, which were ascribed by the Investigator as effects from the SARS-CoV-2 vaccine that they had received on Day 38. Brain imaging showed no evidence of an intracranial thrombotic or embolic event. The subsequent planned Day 45 visit was conducted on Day 49 and the participant was found to have values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 × upper limit of the normal range (ULN), with no elevation in bilirubin. The participant's AST and ALT values returned to the normal range at Day 60. The changes in AST and ALT levels were judged to be unrelated to SLN360 by the Investigator and were assessed as effects of the SARS-CoV-2 vaccine.

Serious AEs (SAEs) were experienced by one (3.1%) participant who received SLN360 30 mg, assessed by the Investigator to be unrelated to study drug.

Transient, dose-dependent increases in C-reactive protein occurred at 12 hours and 24 hours, with the greatest increase occurring in the 600 mg dose group. Neutrophil count also increased during the first 24 hours. These changes were observed predominantly at the higher doses.

The safety assessments for the SAD cohorts are detailed in Table 3.

[redacted]

Table 3 Treatment-emergent and serious adverse events in the single ascending dose part of the first-in-human study of SLN360 (SLN360-001)

Adverse Events by Type	SLN360 30 mg (N=6)	SLN360 100 mg (N=6)	SLN360 300 mg (N=6)	SLN360 600 mg (N=6)	Placebo (N=8)
Number (%) of participants with any TEAE	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (75.0)
TEAE occurring in >3 participants, n (%)					
Headache	2 (33.3)	1 (16.7)	0 (0)	5 (83.3)	1 (12.5)
Diarrhoea	1 (16.7)	0 (0)	0 (0)	1 (16.7)	1 (12.5)
Arthralgia	1 (16.7)	0 (0)	1 (6.7)	1 (16.7)	0 (0)
Neutrophil count increased	0 (0)	0 (0)	0 (0)	3 (50.0)	0 (0)
CRP increased	0 (0)	0 (0)	0 (0)	4 (66.7)	0 (0)
Injection site TEAEs, n (%) E[a]	5 (83.3) 5	6 (100.0) 6	5 (83.3) 5	6 (100.0) 11	1 (12.5) 1
Grade 1	5 (83.3) 5	6 (100.0) 6	4 (66.7) 4	2 (33.3) 3	1 (12.5) 1
Grade 2	0 (0)	0 (0)	1 (16.7) 1	4 (66.7) 8	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any SAEs, n (%)[b]	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)

CRP=C-reactive protein; E=events; n=number of participants, percentages are based on N; SAE=serious adverse event; TEAE=treatment-emergent adverse event

a. Summary by grade using the Common Terminology Criteria for Adverse Events version 5.0

b. Participant visited the Accident and Emergency department for headache following the SARS-CoV-2 vaccine on Day 45 and the participant was hospitalised for cholecystitis and associated signs/symptoms on Day 110

Note: SAE cases were considered unrelated to study treatment.

Longer exposure and repeat dosing will be required to assess the duration of changes to PD parameters and to evaluate the safety of SLN360 further. The MD portion of the study is ongoing.

1.1.4. Study Conduct

This study will be conducted in accordance with the requirements of this Clinical Study Protocol and associated study documents and also in accordance with the following:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)
- Local laws and regulations
- Any amendments to these regulations

[redacted]

1.2. Rationale

Given the weight of evidence from genetic and observational epidemiology and findings from large outcomes trials of LDL-C-lowering drugs [Schwartz *et al*, 2018; Robinson *et al*, 2015], pharmacological lowering of Lp(a) has the potential to reduce risk of ASCVD events. The independence of Lp(a) from established ASCVD risk factors, such as LDL-C, further strengthens the likely benefit of Lp(a)-lowering therapy for individuals whose atherosclerotic disease is driven predominantly by Lp(a). SLN360 is anticipated to offer a clinically important reduction in ASCVD risk in those who have had a previous ASCVD event and those at high risk of a first event, i.e., with both secondary and primary preventive intent.

Data from the United Kingdom Biobank, a longitudinal study of 500,000 adults, demonstrated a strong prospective association of elevated Lp(a) (equal to or greater than 150 nmol/L) with risk of ASCVD events. Elevated Lp(a) was present in 12.2% of those without and 20.3% of those with pre-existing ASCVD and associated with hazard ratios of 1.50 (95% CI, 1.44–1.56) and 1.16 (95% CI, 1.05–1.27), respectively [Patel *et al*, 2021]. Furthermore, in the Multi-Ethnic Study of Atherosclerosis (MESA) (n = 4512) and Dallas Heart Study (n = 2078) cohorts, presence of coronary artery calcification (as determined by computed tomography coronary imaging) in individuals with elevated Lp(a) were strongly predictive of incident ASCVD events (hazard ratio 4.71; 95% CI 3.01 to 7.40 with the highest degree of calcification). Subjects with the lowest level of calcification (score of 1-99) had at least x 2-fold increase in risk [Mehta *et al*, 2022]. In summary, elevated Lp(a) is a likely risk amplifier both in subjects with a prior history of ASCVD and those without established ASCVD. Pharmacological lowering of elevated Lp(a) is anticipated to be beneficial to both these groups.

No data are yet available from an outcome trial of a specific Lp(a)-lowering therapy and the absolute or relative reduction in Lp(a) required to achieve a given reduction in ASCVD risk is unknown. The aim of the proposed Phase 2 study is to characterise the dosing regimen that displays favourable safety and tolerability and has the greatest magnitude and duration of Lp(a) reduction with the lowest dosing frequency in a patient population at high risk of ASCVD events. The weight of observational and genetic epidemiological evidence suggests that optimising the combination of magnitude and duration of Lp(a) lowering is likely to confer the greatest clinical benefit with respect to ASCVD risk reduction.

1.3. Potential Risks and Benefits to Human Participants

Despite Lp(a) being a prevalent genetic risk factor for onset and progression of several manifestations of CVD [Tsimikas *et al*, 2018], there are no approved therapeutics designed to specifically 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 circulating Lp(a) concentration [Arsenault *et al*, 2018; Raal *et al*, 2016].

[redacted]

The eligibility threshold in this study of 125 nmol/L for Lp(a) has been selected to optimise the benefit: risk balance for participants enrolled in the proposed study. In observational cohorts, the inflection in risk of major adverse cardiovascular events appears at Lp(a) concentrations of approximately 30 mg/dL (75 nmol/L) [Emerging Risk Factors Collaboration, 2009]. European [Cegla *et al*, 2019] and United States clinical guidelines [Grundy *et al*, 2019] state that Lp(a) levels over approximately 50 mg/dL (circa 125 nmol/L) as conferring increased CVD risk. European guidance also notes that Lp(a) greater than 150 nmol/L is used as the threshold for offering plasma apheresis in countries where this procedure is available. Data from contemporary trials with PCSK9 inhibitors data suggest that the risk of major adverse cardiovascular events and major adverse limb events is favourably modified above median Lp(a) levels of approximately 15 mg/dL (38 nmol/L) (FOURIER) or 21 mg/dL (52 nmol/L) (ODYSSEY) studies [Szarek *et al*, 2020; O'Donoghue *et al,* 2019]. In addition, to date there is no known adverse phenotype associated with low Lp(a) levels. Therefore, 125 nmol/L has been selected as the eligibility threshold in this study to enrol those participants with the greatest potential to benefit from Lp(a)-lowering treatment with SLN360 and to include a broader population than that studied in the Phase 1 study.

Early safety, PK and pharmacology data from the SAD portion of the ongoing FIH study on SLN360 indicate that TEAEs were generally mild, and the most commonly reported TEAEs were low grade injection site events. Participants were administered a single dose of SLN360 up to 600 mg. Contrastingly, the maximum dose of SLN360 in the proposed study is lower (450 mg) and participants will receive study treatment with at least a 16-week gap between the two doses. Therefore, there are no expected risks to participants in terms of treatment doses or dose scheduling.

The promising early safety results from the ongoing FIH study of SLN360 suggest that the clinical benefits of SLN360 outweigh the anticipated risks. Subsequently, SLN360 could be a safe and effective treatment to lower Lp(a) and its associated cardiovascular risks in individuals with limited alternative treatment options.

2. OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the effect of SLN360 on circulating levels of Lp(a) in participants with elevated Lp(a) at high risk of ASCVD events.

2.2. Secondary Objectives

The secondary objectives are to:

- Evaluate safety and tolerability of SLN360 in participants with elevated Lp(a) at high risk of ASCVD events

[redacted]

- Evaluate the effects of SLN360 on LDL-C and apoB in this population

2.3. Exploratory Objective

The exploratory objective is to evaluate the pharmacogenetic effects of germline genetic variation(s) in response to SLN360.

3. ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is the time-averaged change in Lp(a) from baseline to Week 36.

3.2. Secondary Endpoints

3.2.1. Safety

The secondary safety endpoint is the safety and tolerability of SLN360, as assessed by:

- Adverse event reports
- Physical examination findings
- Twelve-lead ECGs
- Vital signs
- Laboratory safety evaluations

3.2.2. Pharmacodynamics and Efficacy

The secondary PD and efficacy endpoints are:

- The change (time-averaged and by visit) in Lp(a) from the Day 1 pre-dose assessment to Week 48
- The change (time-averaged and by visit) in Lp(a) from the Day 1 pre-dose assessment to Week 60
- The change (time-averaged and by visit) in other lipids/lipoproteins, including LDL-C and apoB, from the Day 1 pre-dose assessment to Week 36
- The change (time-averaged and by visit) in other lipids/lipoproteins, including LDL-C and apoB, from the Day 1 pre-dose assessment to Week 48
- The change (time-averaged and by visit) in other lipids/lipoproteins, including LDL-C and apoB, from the Day 1 pre-dose assessment to Week 60

[redacted]

3.3. Exploratory Endpoints

The exploratory endpoints are the pharmacogenetic effects of germline genetic variation on response to SLN360, measured by association analysis of genetic variants with markers of SLN360 efficacy, including change in Lp(a).

4. STUDY DESIGN

4.1. Summary of Study Design

4.1.1. Study Design

This is a multi-centre, randomised, double-blind, placebo-controlled Phase 2 study to investigate the efficacy, safety and tolerability of SLN360 in participants with elevated Lp(a) at high risk of ASCVD.

The study will be divided into three study periods, comprising screening, treatment and follow-up. An end-of-study (EoS) visit will be conducted to perform final safety and efficacy assessments.

Eligible participants will receive either placebo or SLN360 and will be randomised in the ratio 1:1:2:2:2 into five treatment groups:

- Group 1: Placebo administered subcutaneously at Weeks 0, 16 and 32 (dosing every 16 weeks [Q16W])
- Group 2: Placebo administered subcutaneously at Weeks 0 and 24 (dosing every 24 weeks [Q24W])
    - This group will be stratified so that half of participants are dosed to match the 300 mg Q24W SLN360 group and half are dosed to match the 450 mg Q24W SLN360 group) with respect to injected volume
- Group 3: SLN360 300 mg administered subcutaneously at Weeks 0, 16 and 32 (Q16W)
- Group 4: SLN360 300 mg administered subcutaneously at Weeks 0 and 24 (Q24W)
- Group 5: SLN360 450 mg administered subcutaneously at Weeks 0 and 24 (Q24W)

Placebo

The placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related. The placebo is used since no appropriate active comparator is available; notably, there being no approved pharmacotherapy available that has been shown to yield a clinically meaningful lowering of Lp(a) in people with elevated levels.

[redacted]

Dose groups and treatment regimens are summarised in Table 4.

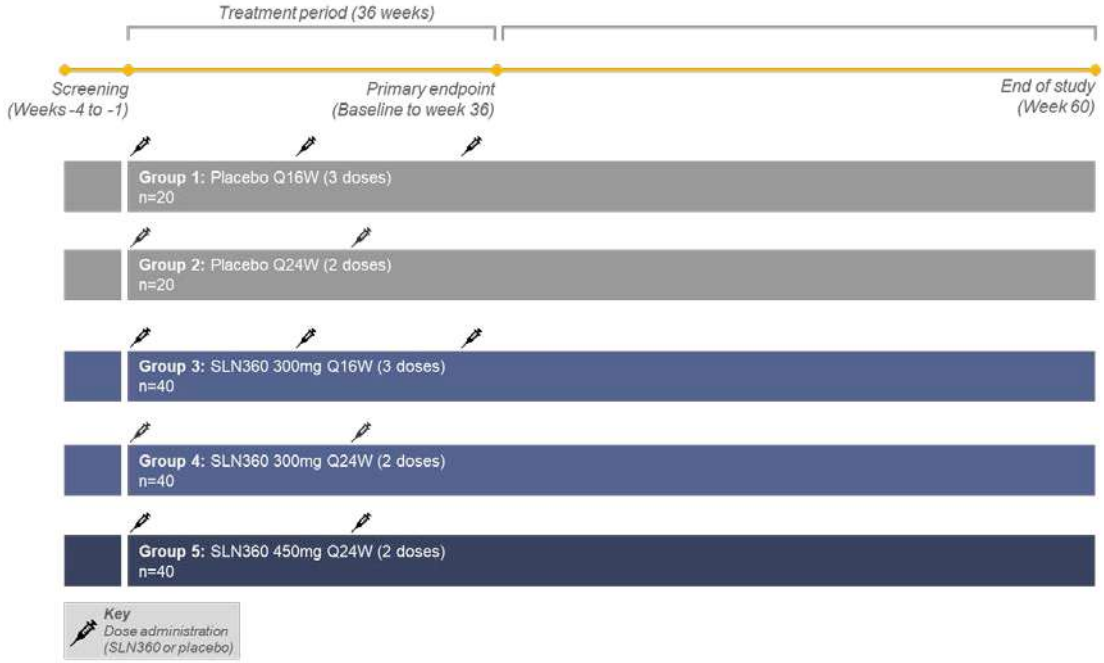
Table 4 Dose groups and treatment regimens for the proposed Phase 2 study

Group	Regimen	No. of SLN360 doses	Total cumulative SLN360 administered
1	Placebo Q16W	-	-
2	Placebo Q24W	-	-
3	SLN360 300 mg Q16W	3	900 mg
4	SLN360 300 mg Q24W	2	600 mg
5	SLN360 450 mg Q24W	2	900 mg

Q16W=dosing every 16 weeks; Q24W=dosing every 24 weeks

An overview of the trial is presented in Figure 2.

Figure 2 Overview of the Phase 2 study



Q16W=dosing every 16 weeks; Q24W=dosing every 24 weeks

Details of all dosing and assessment timepoints are outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

4.1.2. Randomisation and Blinding

All participants will be centrally randomised using interactive response technology (IRT).

This will be a double-blind study, i.e., participants, investigators and specific academic personnel and the Contract Research Organisation (CRO) along with Sponsor staff will be blinded to treatment group allocation. The nature of the treatment supply means that the Pharmacist will be unblinded with appropriate unblinded oversight in place; details will be provided in the Study Blinding Plan.

This design is appropriate since the principal marker of efficacy (serum Lp[a] concentration) is an objective laboratory measure that is negligibly susceptible to bias and not influenced by potential confounders such as diet and physical activity. Blinding participants and investigators will ensure the robustness of the safety and tolerability assessments of SLN360.

4.1.3. Duration of Participant Participation

There are a planned minimum of 15 visits for each participant, including screening. The maximum expected duration of participation for an individual participant will be up to 64 weeks. This includes a screening period of up to 4 weeks, a treatment period of up to 36 weeks and a follow-up period of up to 24 weeks, reaching EoS at Week 60.

Primary analysis will be performed once all participants have completed 36 weeks of treatment.

4.2. Study and Participant Termination

Changes in the health status of the participant since the screening visit, including laboratory results, will be checked prior to administration of the study treatment. Participation of a participant in this clinical study will be discontinued for any of the following reasons:

- Withdrawal of consent
- Termination of the study by the Sponsor or a regulatory authority

Participants are free to withdraw consent from the study (which means permanent discontinuation of study drug administration and all follow-up assessments) at any time without prejudice. Note that discontinuation of study drug in and of itself is not considered withdrawal of consent.

The Investigator must temporally interrupt or permanently discontinue study treatment for the participant if administration is believed to be contrary to the best interests of the participant; further details are provided in Section 10.2.3.

[redacted]

5. STUDY POPULATION

5.1. Participants

In this trial the inclusion of a high-risk population defined by coronary artery calcification (inclusion criterion 4g) offers an opportunity to investigate the effect of Lp(a)-lowering treatment in a group of patients with at least a x 2-fold increase risk of ASCVD as demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA) and Dallas Heart Study [Mehta *et al*, 2022]. As GalNAc siRNA is a highly targeted approach there are no anticipated differences in safety and efficacy that will be evaluated in this study in the proposed broad population'

Approximately 160 participants are planned to be recruited at approximately 40 centres worldwide. Each placebo group will include 20 randomly allocated participants, and each SLN360 group will include 40 randomly allocated participants. This will result in a total of 120 participants exposed to SLN360 and 40 participants exposed to placebo.

The number of participants assigned to each treatment group is summarised in Table 5.

Table 5 Treatment groups and planned number of participants

Group	N	Planned dose	Dosing regimen	Total participants
1	20	Placebo	Q16W	160 (120 SLN360, 40 placebo)
2[a]	20	Placebo	Q24W	
3	40	SLN360 300 mg	Q16W	
4	40	SLN360 300 mg	Q24W	
5	40	SLN360 450 mg	Q24W	

Q16W=dosing every 16 weeks; Q24W=dosing every 24 weeks

a. Group 2 will be stratified so that half of participants receive 1.5 mL placebo (to match the volume of the 300 mg SLN360 dose) and half receive 2.25 mL placebo (to match the volume of the 450 mg SLN360 dose)

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria are met:

1. Male or female
2. Aged 18 to 80 years inclusive at screening
3. Lipoprotein(a) at screening equal to or greater than 125 nmol/L
4. At high risk of ASCVD, i.e., at least one of the following conditions:
   a. Previous MI

[redacted]

b. Coronary angiographic diagnosis of CAD with or without previous MI

c. Computerised tomography/magnetic resonance imaging diagnosis of CAD with or without previous MI

d. Previous coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft)

e. Prior ischeamic stroke as previously confirmed by a documented brain imaging study (e.g. computed tomography or magnetic resonance imaging brain), and considered not to be caused by thromboembolic phenomena associated with atrial fibrillation, valvular heart disease or mural thrombus

f. Peripheral arterial disease

g. Existing evidence of coronary artery calcium on computerised tomography (coronary artery calcium score ≥1 AU)

5. A body mass index at screening in the range 18.0 to 32.0 kg/m^2, inclusive
6. Participants must be able to provide valid informed consent and to comply with all study requirements
7. Participants receiving lipid-modifying therapy (including statins, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, ezetimibe) must be on a stable, maximum tolerated regimen, according to the clinical judgement of the Investigator, at screening (i.e., receiving therapy for a minimum of 8 weeks) with no changes to existing regimens or introduction of new regimens made after screening. For monoclonal antibody PCSK9 inhibitors, a stable dose is defined as at least four doses at a consistent dose level

5.2.2. Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria are met:

1. Cardiovascular disease-related:
   a. Acute cardiovascular event within the 12 weeks before screening (including but not limited to acute MI, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, stroke, acute limb ischaemia, limb revascularisation)
   b. Planned or expected cardiac surgery or coronary or other revascularisation within 12 weeks of screening or planned major non-cardiac surgery during the study period
2. Medical history:
   a. Renal dysfunction with estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 (according to the Chronic Kidney Disease Epidemiology Collaboration equation) at screening

[redacted]

b. Acute, chronic or historical liver disease, including viral hepatitis (hepatitis A, B or C virus) at screening. Participants with positive hepatitis B virus surface antibody titre reflecting hepatitis B virus immunisation are permitted to participate

c. Hepatic dysfunction based on liver function markers at screening: AST, ALT or total bilirubin >2 × ULN

d. Established diagnosis of Gilbert syndrome

e. Inherited or other bleeding disorders

f. Malignancy (except non-melanoma skin cancers, cervical *in situ* carcinoma, breast ductal carcinoma *in situ*, stage 1 prostate carcinoma, or benign tumours) within the 5 years before screening

g. Current or previous history of moderate to severe heart failure (New York Heart Association Functional Classification grade III or IV at screening) or last known left ventricular ejection fraction less than 30% at screening

h. Ventricular tachycardia, atrial fibrillation with rapid ventricular response or supraventricular tachycardia that are not controlled by medications in the 12 weeks before screening

i. Fasting triglycerides >400 mg/dL (4.5 mmol/L) at screening

j. Uncontrolled hypertension at screening, defined as an average sitting systolic blood pressure >160 mmHg or an average diastolic blood pressure >110 mmHg after a minimum of three measurements

k. Type 1 diabetes mellitus or poorly controlled (glycated haemoglobin ≥10% or ≥86 mmol/mol) type 2 diabetes mellitus at screening

l. Known active infection or major haematological, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the Investigator at screening or Day 1

3. Concomitant medication:

a. Currently receiving or <12 weeks at Day 1 since receiving >200 mg/day niacin or niacin derivative drugs (e.g., niceritrol, nicomol)

b. Treatment with lipid/lipoprotein apheresis within the 12 weeks before screening

c. Treatment with a cholesteryl ester transfer protein inhibitor (e.g., anacetrapib, dalcetrapib, evacetrapib, obicetrapib) or lomitapide within the 52 weeks before screening

d. Treatment with aspirin, clopidogrel, ticagrelor or other antiplatelet agent unless prescribed at a low maintenance dose for the purpose of cardiovascular risk reduction (i.e., aspirin up to 325 mg daily, clopidogrel 75 mg daily, ticagrelor 180 mg daily)

[redacted]

e. Participation in another clinical trial including an investigational medicinal product (IMP) within 12 weeks, or within five half-lives of that IMP, before screening

f. Any previous use of approved or experimental siRNA therapy (e.g., inclisiran). NB: use of mRNA-based vaccines for infectious diseases is permitted

g. Use of approved or experimental antisense oligonucleotide therapy within the 24 weeks before screening. NB: use of mRNA-based vaccines for infectious diseases is permitted

h. Use of experimental Lp(a)-reducing therapy within the 52 weeks before screening

i. Use of herbal or complementary medicines, dietary supplements or vitamins known to substantially influence lipid metabolism or blood lipid or lipoprotein levels (e.g., fish oil, turmeric, red yeast rice) within the 4 weeks before Day 1

4. Alcohol and illegal drugs:

   a. History or clinical evidence of alcohol misuse within the 26 weeks before screening

   b. History or clinical evidence of recreational drug use within the 26 weeks before screening

5. Other exclusions:

   a. Female participants of childbearing potential with a positive serum pregnancy test assessed at screening or positive urine pregnancy test on Day 1

   b. Female participants of childbearing potential planning to become pregnant or breastfeed during treatment and for an additional 12 weeks after the last dose of study treatment

   c. Female participants of childbearing potential unwilling to use a highly effective method of contraception during treatment and for an additional 12 weeks after the last dose of study treatment

   d. Male participants must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the participant must be using a highly effective contraception method from the time of signing the informed consent form (ICF) until at least 12 weeks after the last dose of study treatment

   e. Known sensitivity to any of the products to be administered during dosing

   f. Likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the participant and Investigator's knowledge

   g. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the

[redacted]

Investigator or Sponsor, if consulted, would pose a risk to participant safety or interfere with the study evaluation, procedures or completion

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Screening

Once informed consent has been obtained, participants will undergo a screening assessment to see if they are suitable to be enrolled in the study. Screening visits will be conducted by the Investigator or their appropriately qualified designee. Screening may be performed up to 28 days before first treatment administration.

For clinical sites without access to existing Lp(a) data for potentially eligible participants, participants may complete an optional pre-screening visit to evaluate Lp(a) levels. At this optional pre-screening visit, sites may send blood samples to a local laboratory to measure Lp(a) levels, thereby supporting the identification of eligible participants that may proceed into screening. The optional pre-screening visit may be conducted up to 14 days prior to the screening visit. A separate pre-screening ICF is available for this purpose. Participants may choose to forego the optional pre-screening ICF and only sign the main study ICF. All patients will need to sign the main study ICF before proceeding with study-related screening assessments.

6.2. Medical History

The participant's medical history will be collected by the Investigator or suitably qualified designee. The information will be collected from the participant and/or their medical records and should include all ongoing and past diseases or conditions identified as relevant by the Investigator. The participant should be excluded from the trial if any disease or condition listed in the exclusion criteria is detected. Particular attention should be paid to the following conditions/diagnoses:

- Renal dysfunction
- Acute, chronic or historical liver disease
- Hepatic dysfunction
- Inherited or other bleeding disorders
- Malignancy
- Heart failure or heart abnormalities
- Hypertension
- Diabetes mellitus
- Active infection

[redacted]

- Other haematological, renal, metabolic, gastrointestinal or endocrine dysfunction

The Investigator or designee should record the date in which comorbidities began (where known).

Any relevant diagnostic, therapeutic or surgical procedures or those performed in the 10 years before screening must be recorded in the electronic case report form (eCRF), including the dates, indication, description of the procedure(s) and any clinical findings, if applicable. Other procedures performed greater than 10 years before screening but relevant to eligibility criteria, safety considerations or otherwise clinically relevant should also be recorded.

6.3. Demographics

The following demographic information should be recorded:

- Age
- Sex
- Race
- Ethnicity

Information that could identify the participant, such as name, initials, social security number (if applicable), (national) insurance number, etc., should not be recorded in the eCRF and should not be transmitted from the site to the Sponsor.

6.4. Pharmacodynamic and Efficacy Procedures

SLN360 PD will evaluate Lp(a) levels as the most proximal measurable marker reflecting target engagement. Lipoprotein(a) will be measured centrally using a molar assay. On dosing days, blood samples for PD biomarkers should be collected pre-dose. Of note, the full set of parameters listed may not be assessed at every timepoint described in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

Biomarkers to be measured include:

- Serum lipids and lipoproteins
  - Lipoprotein(a)
  - Apolipoprotein B
  - Low-density lipoprotein cholesterol
  - High-density lipoprotein cholesterol
  - Total cholesterol
  - Triglycerides

[redacted]

- Oxidised phospholipids
- C-reactive protein

All biomarkers will be measured centrally. Blood samples will be collected for biomarker evaluations at the times indicated in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

6.5. Safety Procedures

6.5.1. Adverse Event Assessments

Information regarding the occurrence of AEs for each participant will be collected from the time a signed and dated ICF for the main study is obtained until completion of the participant's last study-related procedure, which may include contact to follow-up for safety. Adverse events that start from the time the participant signs the main study ICF until treatment administration on Day 1 will be assigned as non-treatment emergent AEs; AEs starting or worsening after treatment administration will be recorded as TEAEs. See the Time and Events tables (Appendix 15.1 and Appendix 15.2) for detailed timing of assessments. Grading of AEs is outlined in Section 11.2.

6.5.2. 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 injection sites monitored throughout the study. Inspection of the site of administration and surrounding area will be performed at timepoints specified in the Time and Events tables (Appendix 15.1 and Appendix 15.2). Injection site reactions should be followed up until resolution. Should an ISR not be resolved at the end of a study visit, the Investigator should maintain frequent contact, either in person or remotely, with the patient to confirm the course and the date of resolution. Additional evaluations of the injection site may be performed if a reaction is observed, at the discretion of the Investigator. The following information will be collected at all ISR assessments:

- Pain: Yes/No
- Tenderness: Yes/No
- Redness/erythema: Yes/No
  - If ‘Yes’, measurement of the largest dimension to be recorded in centimetres
- Swelling/induration: Yes/No
  - If ‘Yes’, measurement of the largest dimension to be recorded in centimetres

[redacted]

All ISRs are to be recorded as an AE if they meet AE criteria and an overall rating for each ISR will be recorded using the specific scale described in NCI-CTCAE v5 (Table 6).

Table 6 Injection site reaction grading scale

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Injection site reaction (ISR)	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; oedema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences: urgent intervention indicated	Death

6.5.3. Twelve-Lead Electrocardiogram

Twelve-lead ECGs should be performed at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2) in a standardised manner, that is, after the participant has rested in the semi-supine position for at least 10 minutes. Measurements will be made using an ECG machine that automatically calculates the heart rate, PR interval, QRS interval, RR interval and QT interval. All ECG traces will be reviewed and signed by the Investigator or designee, and any abnormalities will be marked as clinically significant or not clinically significant. If the average QT interval corrected using Fridericia's formula (QTcF) is ≥500 milliseconds, then an additional ECG should be repeated after at least a 5minute interval. If the participant has a permanent pacemaker *in situ*, the effects of pacing on the QTcF should be taken into account.

6.5.4. Vital Signs

Vital signs (temperature, respiratory rate, heart rate and systolic and diastolic blood pressure) will be assessed at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2). Participants should rest in a supine position for 10 minutes before the vital signs are assessed. Vital signs may be repeated once after at least a 5-minute interval if obtained values are abnormal or outside the normal range at first measurement.

The participant's weight will be measured at each timepoint (without shoes or heavy garments [e.g., coats, jumpers]). The participant's height will only be measured at the screening visit.

[redacted]

6.5.5. Physical Examination

Full or abbreviated physical examinations will be performed by a qualified clinician at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2), as described below.

- Full physical examination at screening, pre-dose on Day 1 and EoS: the Investigator or appropriately qualified designee will examine and/or measure height and weight and the skin, eyes, ears, mouth, lymph nodes, respiratory, cardiovascular, gastrointestinal, neurological and musculoskeletal systems
- Abbreviated physical examination at subsequent visits: the assessment will be focused and guided by symptoms reported by the participant, 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

6.5.6. Laboratory Assessments

6.5.6.1. Haematology and Coagulation

Blood for the assessment of haematology parameters will be collected at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2). Of note, the full set of parameters listed may not be assessed at every timepoint described in the Time and Events tables.

The following parameters will be assessed during the study:

- Red blood cell count
- Haematocrit
- Mean corpuscular volume
- Haemoglobin concentration
- Platelet count
- White blood cell count
- Neutrophil count and percentage
- Lymphocyte count and percentage
- Monocyte count and percentage
- Eosinophil count and percentage
- Basophil count and percentage

[redacted]

- Prothrombin time
- Activated partial thromboplastin time
- International normalised ratio
- Fibrinogen concentration
- Plasminogen activity
- Plasminogen concentration
- Haemoglobin A_{1C}

Blood samples will be analysed centrally, and some samples will be retained for further analysis. Further details on processing can be found in the Laboratory Manual.

6.5.6.2. Clinical Chemistry

Blood for the assessment of clinical chemistry parameters will be collected at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2). Of note, the full set of parameters listed may not be assessed at every timepoint described in the Time and Events tables.

The following parameters will be assessed:

- Creatinine
- Urea
- Estimated glomerular filtration rate (using Chronic Kidney Disease Epidemiology Collaboration equation)
- Sodium
- Potassium
- Calcium
- Chloride
- Inorganic phosphate
- Creatine kinase
- Alanine aminotransferase
- Aspartate aminotransferase
- Alkaline phosphatase
- Gamma-glutamyl transferase
- Total bilirubin
- Direct bilirubin

[redacted]

- Total protein
- Albumin
- Glucose
- C-reactive protein
- Beta-human chorionic gonadotrophin
- Thyroid stimulating hormone
- Triiodothyronine
- Thyroxine

Blood samples will be analysed centrally, and some samples will be retained for further analysis. Further details on processing can be found in the Laboratory Manual.

6.5.6.3. Viral serology

Blood samples will be collected at screening for detection of hepatitis A, B and C and human immunodeficiency virus. The following parameters will be assessed:

- Hepatitis A serology
- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C antibody
- Human immunodeficiency virus 1 and 2 serology

6.5.6.4. Anti-drug antibodies

Blood samples will be collected for assessment of SLN360 anti-drug antibodies at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

6.5.6.5. Urinalysis

Urine samples will be collected at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

The following parameters will be assessed at each timepoint:

- Leukocytes
- Glucose
- Ketones
- Nitrite

[redacted]

- Bilirubin
- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen

Urine samples will be analysed locally using a dipstick but may also be analysed centrally if indicated and deemed appropriate by the Investigator.

6.5.7. Pregnancy Testing and Reporting

Women of child-bearing potential must have a negative pregnancy test at screening. A pregnancy test will be performed at the times indicated in the Time and Events tables (Appendix 15.1 and Appendix 15.2). Following administration of study drug, any known cases of pregnancy in female patients or in pregnant partners of male patients will be reported until 3 months after study completion. It is the responsibility of the Investigator, or designee, to report any pregnancy and anticipated date of birth that occurs while a patient is receiving the study drug via the *in utero* exposure form. If the pregnancy is to be terminated, the anticipated date of termination should be provided.

The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours. The pregnancy must be followed up within 30 days regardless of the outcome (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) and status of mother and child, even if the patient was discontinued form the study. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report.

If the Investigator becomes aware of a pregnancy occurring in the partner of a patient participating in the study, the pregnancy should be reported to the Sponsor (or designee) within 24 hours. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. If consent is provided, the pregnancy of the partner should be followed by the Investigator until completion of the pregnancy.

6.6. Pharmacogenetic Procedures

Pharmacogenetic effects of germline genetic variation on Lp(a) response to SLN360 will be measured from a blood sample by association analysis of genetic variants with markers of SLN360 efficacy at times indicated in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

[redacted]

6.6.1. Genotyping

Blood samples will be collected at the times outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2) for genotyping to enable generation of genetic data for exploratory pharmacogenetic analysis.

6.7. Independent Data Monitoring Committee

6.7.1. Role of the Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is responsible for review of data during the study. The IDMC will review accrued data on an ongoing basis and make relevant recommendations to the Sponsor. The IDMC is an independent group of experts in clinical trials, clinical medicine and drug safety. The details of the role, remit and responsibility of the IDMC, together with practical considerations for data review and IDMC meetings are provided in the IDMC Charter.

6.7.2. Independent Data Monitoring Committee Composition

The IDMC is composed of experts who are independent of the Sponsor and CRO. The expertise of members will cover medical aspects of clinical trial conduct in CVD, cardiovascular medicine, oligonucleotide therapeutics and drug safety.

6.7.3. Data Available for Independent Data Monitoring Committee Review

The IDMC will primarily review semi-blinded data from this Phase 2 study. Where necessary, to enable interpretation of the data and to make a recommendation to the Sponsor, the IDMC may review unblinded data; the minimum necessary amount of data to enable decision-making should be unblinded to maintain the scientific integrity of the study. The IDMC may also review accrued data from the ongoing Phase 1 (APOLLO) study.

6.7.4. Independent Data Monitoring Committee Recommendations and Meeting Schedule

The IDMC will provide recommendations on specific questions of study conduct deemed appropriate by the IDMC or Sponsor. The meeting schedule will be defined in the IDMC charter.

[redacted]

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1. Lifestyle and Dietary

The following lifestyle and dietary restrictions apply throughout the study:

- Participants should not consume alcohol within the 48 hours before and until 48 hours after each dose administration
- Participants should not consume more than 14 units of alcohol per week. A unit is defined as one measure (25 mL) of spirits, half a pint (236 mL) of standard-strength beer or one small glass (125 mL) of wine
- Participants should not use recreational drugs unless prescribed by a physician
- Participants are required to refrain from strenuous exercise for 24 hours before and 24 hours 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 programme nor participate in any unusually strenuous physical exertion)

7.2. Contraception

7.2.1. Female Participants

Female participants who are of childbearing potential (who are heterosexually active) must agree to use a highly effective method of contraception from the start of the screening period until 12 weeks after the last administration of study drug.

Methods with a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods, and include:

- Combined (oestrogen and progestogen containing) hormonal contraception association 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
- Vasectomised partner (provided that the partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical confirmation of surgical success)

[redacted]

- 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 participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods), declaration of abstinence for the duration of exposure to study treatment and withdrawal are not acceptable methods of contraception

All women are to be considered of childbearing potential unless they are permanently sterile or postmenopausal. A woman must only be considered permanently sterile if they have clear medical documentation confirming hysterectomy, bilateral salpingectomy or bilateral oophorectomy. 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 postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.

7.2.2. Male Participants

Male participants must use a male condom (with or without spermicide) if sexually active with a female of childbearing potential from the start of the screening period until 12 weeks after the last administration of study drug. Male participants should be encouraged to inform their female sexual partners that they are participating in a Phase 2 clinical study.

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

8. INVESTIGATIONAL PRODUCT(S)

8.1. Dosage and Administration

SLN360 is provided as a solution for injection for subcutaneous use in glass vials. A vial (2R vial) contains 0.5 mL (extractable volume) of an aqueous sterile solution of SLN360 drug substance with a concentration of 200 mg/mL (as free acid form). The vials are intended for single use. SLN360 will be supplied by the Sponsor or designee, along with the batch/lot numbers and Certificates of Analysis.

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

[redacted]

Individual injection volume at each injection site will not exceed 1.5 mL, and up to two 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 ideally should be separated by a few centimetres, according to local practice. When multiple injections are given, injection sites should be rotated to a different location (i.e., not administered in precisely the same place for subsequent administrations) and a new quadrant of the abdomen should be used for each injection. It is recommended to proceed around the quadrants in a clockwise direction. Injection sites should be recorded in the eCRF.

Participants will be dosed at the timepoints outlined in the Time and Events tables (Appendix 15.1 and Appendix 15.2).

8.2. Dose Rationale

Data from SAD administration in the FIH study and from modelling of nonclinical data (LYO-X Report No.: LYO-X-2022-06-0003) indicate that the safe, tolerable and effective doses of SLN360 for evaluation in this Phase 2 study are 300 mg and 450 mg. SLN360 and placebo will be administered via subcutaneous injection in multiple doses. Placebo and three SLN360 dosing regimens will be evaluated: 300 mg Q16W, 300 mg Q24W and 450 mg Q24W.

Efficacy is defined as a combination of magnitude of Lp(a) reduction and the duration over which that reduction persists. Data from the FIH study suggest that a reduction of 80 to 90% in Lp(a) levels from baseline sustained for more than 12 weeks is anticipated at these doses.

8.2.1. Pharmacokinetic-pharmacodynamic Modelling for Dose Selection

Recommended Dose Range:

Safety data from the completed SAD part of the ongoing Phase 1 study support the dose range in this Phase 2 study of 300 to 450 mg based on the summarised data in Section 1.1.3. The 300 mg dose in the SAD part of the Phase 1 study was well tolerated with no concerning treatment-associated safety signals. The maximal dose, 600 mg, was associated with ISRs (up to CTCAE grade 2), all of which resolved. Plasma PK for these doses was broadly dose proportional. From an efficacy perspective, lowering of Lp(a) concentration from baseline by at least approximately 80% is the objective of the SLN360 programme; this magnitude of effect or greater was observed after single doses of 100 mg, 300 mg and 600 mg in the SAD part of the Phase 1 study. Exaggerated pharmacology is not a concern with Lp(a)-lowering as individuals have been identified with near-zero circulating concentrations of Lp(a) and with no reported adverse

[redacted]

consequences. Therefore, the benefit: risk balance based on the available clinical and nonclinical data supports a starting dose of 300 mg in this study.

Maximum Supported Dose:

Data from the SAD part of the Phase 1 study, suggest lower tolerability of the maximum evaluated dose of 600 mg. In brief, ISRs accompanied by transient leukocytosis and rises in C-reactive protein were observed at the 600 mg dose. Considering these findings, we do not intend to pursue the 600 mg dose further in development. However, the SAD Phase 1 data and PK-PD modelling appear to support a favourable benefit: risk when evaluating doses up to 450 mg based on predicted magnitude and duration of Lp(a) lowering for clinical benefit in patients with ASCVD.

Pharmacokinetic-pharmacodynamic Modelling:

The data from the SAD part of the Phase 1 study was used to construct a population PK-PD-based SLN360 model. The model structure was based on modelling of preclinical studies in non-human primates and included a liver compartment and associated liver parameters. A small subset of parameters in the human model were fixed to values allometrically scaled from the non-human primate model, a choice justified by the lack of liver data in humans and the ability of the full non-human primate model predict the Phase 1 data after scaling to human. All model parameters not fixed to values allometrically scaled from non-human primates were estimated using the Phase 1 study PK and PD data.

Data used for the modelling included:

- Non-human primate plasma and liver SLN360 concentrations, serum Lp(a) concentrations
- Human plasma SLN360 and Lp(a) concentration from SAD part of the Phase 1 study for single doses of placebo and 30, 100, 300 and 600 mg of SLN360

Full details of the nonclinical studies are available in the IB. Modelling tested a range of covariates: age, body weight, sex, eGFR (PK estimates only), and baseline Lp(a) (PD estimates only). No covariates were included in the final model used for predictions of PK and PD in this Phase 2 study.

Simulations were prepared for a range of repeat dosing regimens, including but not limited to:

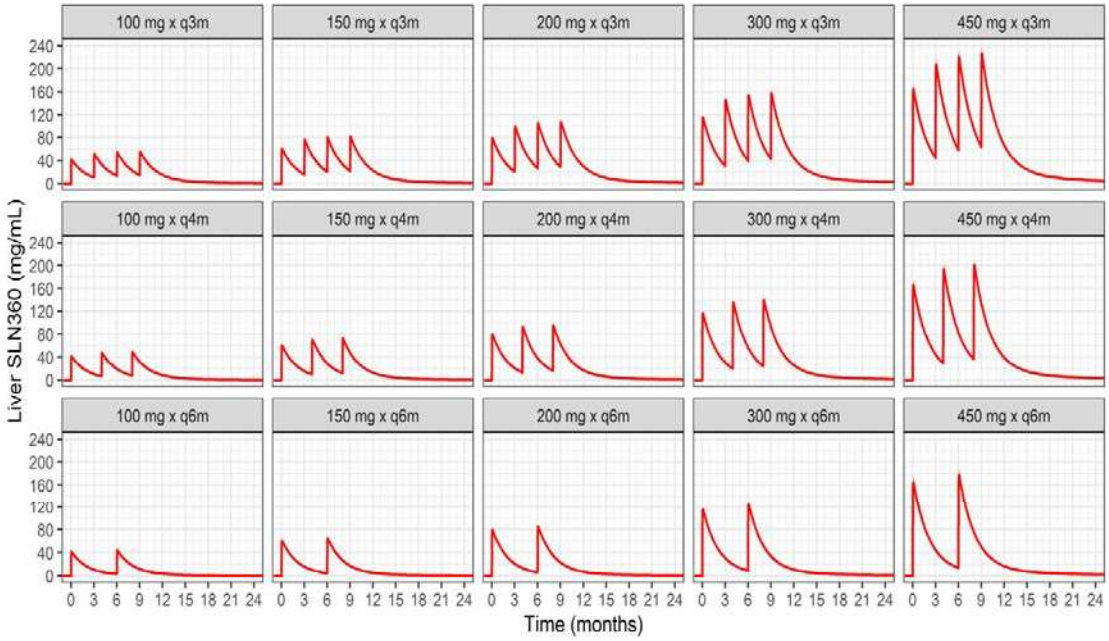
- Three hundred mg dosing every 3, 4 and 6 months (Q3M, Q4M and Q6M, respectively)
- Four hundred and fifty mg Q3M, Q4M and Q6M

[redacted]

Each simulation included 300 individuals, from which were derived the simulated liver concentrations of SLN360, longitudinal profile of Lp(a) change over 24 months and the time-averaged change in Lp(a) over a dosing interval after the final simulated dose.

The simulated SLN360 liver exposure is shown in Figure 3. With repeated dosing, only modest increments in liver exposure are predicted, with the increment diminishing after the second dose.

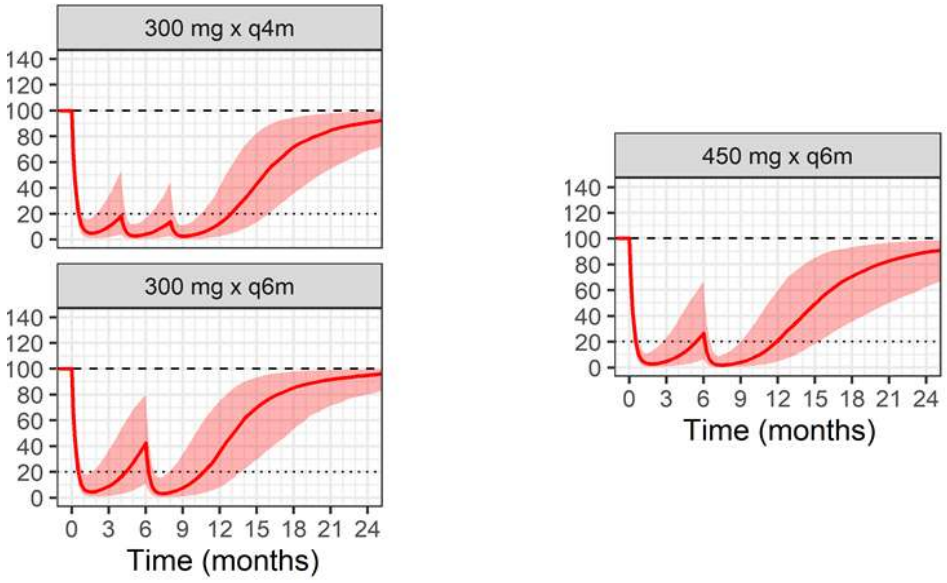
Figure 3 Predicted liver SLN360 concentrations after repeat dosing with a range of doses and regimens



Note: simulated median (red line), 5th and 95th prediction interval (red area) from 300 simulated individual profiles.

The profiles for the dosing regimens proposed for the planned Phase 2 study are in Figure 4.

Figure 4 Simulated serum Lp(a) levels for the dosing regimens planned in the proposed Phase 2 study

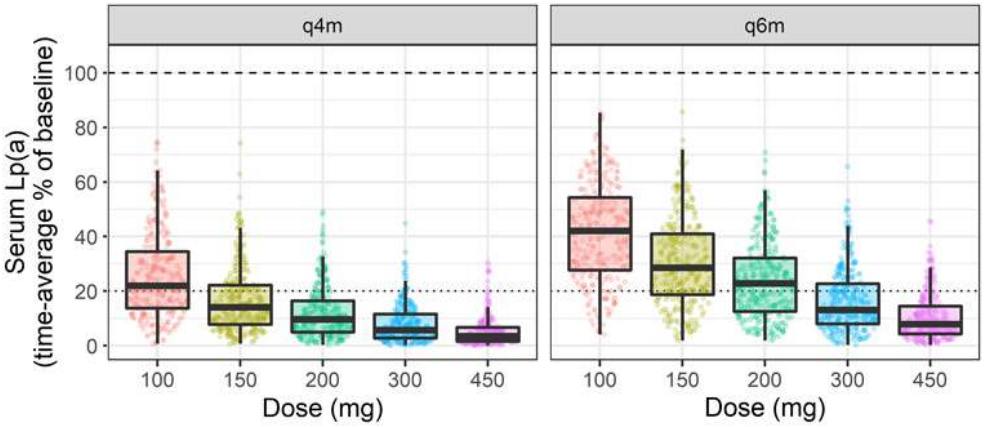


Note: simulated median serum Lp(a) (red line), 5th and 95th prediction interval (red area) from 300 simulated individual profiles. Baseline (dashed line). Target % lowering from baseline = 20% (dotted line).

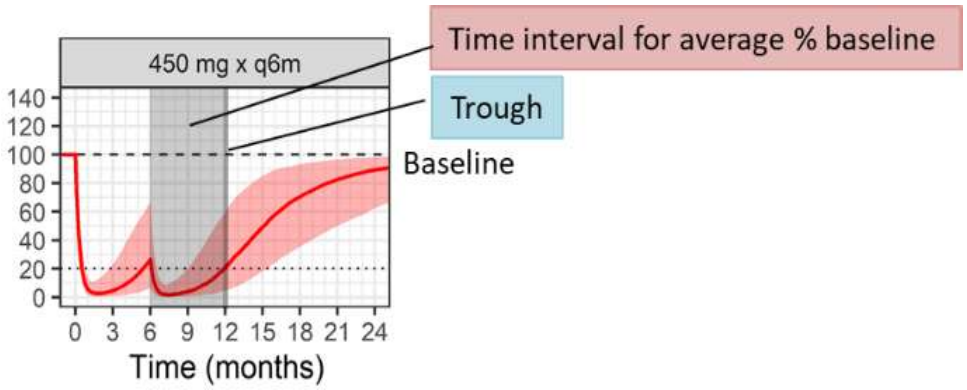
The most clinically meaningful measure of SLN360 efficacy is a function of the magnitude and duration of Lp(a) lowering. This can be quantified by the time-averaged change in Lp(a) after dosing. Figure 5 illustrates the simulated time-averaged change in Lp(a), from 300 simulated individuals. The time period for the average is the change from the last dose administered in each regimen to 12 months. For Q4M regimens this is the period after the third dose and for Q6M regimens it is the period after the second dose. In both cases, the time periods represent a single dosing interval.

Figure 5 Simulated time-averaged change in serum Lp(a) for a range of dosing regimens, including those planned for the proposed Phase 2 study

A



B



Lp(a)=lipoprotein(a); q4m=dosing every 4 months; q6m=dosing every 6 months
A) Serum Lp(a) predicted time-average % change from baseline for dosing interval (after final simulated dose).
B) Illustration of sources of data for time-averaged change in Lp(a). Based on 300 simulated individual profiles. Trough refers to trough exposure for a continuous Q6M dosing interval.

The percentage of the simulated population with time-averaged reduction in Lp(a) >80% lower than baseline values are described in Table 7. The doses planned in the proposed Phase 2 study are highlighted.

[redacted]

Table 7 Percentage of population with time-averaged reduction Lp(a) >80% lower than baseline

	SLN360 Doses				
Regimen	100 mg	150 mg	200 mg	300 mg	450 mg
4 x Q3M	68.7%	85.3%	93.3%	98.7%	99.7%
3 x Q4M	40.7%	69.7%	82.7%	94.0%	97.3%
2 x Q6M	12.3%	29.7%	43.7%	68.7%	86.7%

Q3M=dosing every 3 months; Q4M=dosing every 4 months; Q6M=dosing every 6 months
Cells highlighted in grey indicate the doses to be evaluated in this study.

Based on all of the PK-PD modelling findings, the following conclusions were made:

- Liver exposure reaches near the steady-state after the second dose of SLN360 and substantial liver accumulation is not anticipated with repeat dosing
- Efficacy of SLN360, with respect to Lp(a)-lowering, is meaningfully characterised as a time-averaged change in serum Lp(a) from baseline
- Dosing regimens of 300 mg Q4M, 300 mg Q6M and 450 mg Q6M allow exploration of a dose range that offers the combination of anticipated safety, frequency of administration and time-averaged reduction in Lp(a) that best support a favourable benefit: risk in the target population

8.3. Maintaining the Blind

Participants, Investigators and specific academic personnel and the CRO along with Sponsor staff will be blinded to treatment group allocation. The nature of the treatment supply means that the Pharmacist will be unblinded with appropriate oversight; details will be provided in the Study Blinding Plan.

8.3.1. Emergency Unblinding

Emergency unblinding is defined as a purposeful action to reveal the actual treatment assignment of the study participant whereby the knowledge of the treatment assignment is essential for the clinical management, safety and/or welfare of a specific participant. The Investigator should discuss with the Medical Monitor before unblinding, if possible. The Sponsor must be notified within 24 hours after breaking the blind.

The IRT system that is used for participant 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).

[redacted]

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

- Participant number
- Site number
- Study/protocol number
- Date and time of unblinding
- Reason for unblinding

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

8.4. Treatment Assignment

This is a randomised controlled study; participants will be assigned their treatment using IRT. Participants will be allocated to a treatment group in accordance with the randomisation schedule. The randomisation schedule will be computer generated.

Randomisation (allocation to treatment) will occur just before the participant receives their first dose of study drug. Once assigned, randomisation numbers shall not be reassigned. Randomisation numbers will be assigned and maintained using IRT. Each participant will be allocated a unique participant identifier at screening that will be used throughout the study.

Participants will be randomised in a 1:1:2:2:2 ratio to the groups described in Section 4.1.1 to receive either SLN360 or placebo.

Further details on the randomisation process will be provided in the IMP Handling Manual.

8.5. Packaging and Labelling

Study treatment will be supplied in single-use, pre-filled glass vials that will have been labelled and packaged before distribution to the study sites. Study treatment will be labelled and packaged under the responsibility of the Sponsor. No medication can be re-labelled or repackaged without prior approval from the Sponsor.

Medication will be provided to the sites in an open-label format. The labels will contain all information required to meet the applicable local regulatory requirements. The syringe labels applied following dispensing will be blinded.

Further information on the study drug packaging, labelling and dispensing will be provided in the IMP Handling Manual.

8.6. Preparation

Details on the preparation of SLN360 will be provided in the IMP Handling Manual.

8.7. Handling and Storage

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 (35.6°F) and 8°C (46.4°F).

Placebo treatment (commercial NaCl injection, 0.9% weight/volume administered via subcutaneous 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.

8.8. Product Accountability and Assessment of Compliance

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 authorised by the Sponsor and a certificate of destruction is made available.

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

8.9. Treatment of Investigational Product Overdose

From a primary pharmacological perspective, participants are individuals who have elevated Lp(a) levels and are at high risk of a first ASCVD event. The majority of the general population has low (less than approximately 50 mg/dL) circulating Lp(a) levels [Kamstrup *et al*, 2009]. These low levels are not associated with adverse health outcomes; for instance, individuals with no detectable Lp(a) have been identified, and they display no substantial detrimental effects [Lim *et al*, 2014; Emdin *et al*, 2016]. Therefore, potential harmful effects of 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 IB.

[redacted]

8.10. Occupational Safety

No specific risks have been identified for staff handling the study treatment. The Material Safety Data Sheets will be made available where required by local regulations.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Recording Prior and Concomitant Medication

All concomitant medications, including medication given in the 30 days before study treatment administration and during the study, must be recorded in the eCRF along with the indication for which it was used. The generic name of the drug should be specified along with the dose, frequency, duration and route of administration of treatment.

Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded in the eCRF, including the dates, indication, description of the procedure(s) and any clinical findings, if applicable.

9.2. Permitted Medications

Other than the therapies listed in Section 9.3, the use of any concomitant medication/therapy, including over-the-counter medications that is deemed necessary for treating the participant is permitted during the study. Any medication used for the management of dyslipidaemia (including statins, ezetimibe, bempedoic acid, fibrates, omega-3 fatty acids, colesevelam and implitapide) must have been at a stable, maximum tolerated 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 participants will only be permitted if the therapy has been prescribed at a stable dose for at least 8 weeks prior to screening and is expected to remain stable for the duration of the study (in the opinion of the Principal Investigator).

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

9.3. Prohibited Medications and Procedures

The following concomitant treatments are not permitted during the study:

- Initiation of medication or therapies significantly affecting Lp(a) levels (including but not restricted to PCSK9 inhibitors, prescription dose niacin, fibrates and anti-oestrogen therapy)

[redacted]

- Initiation of statins and/or ezetimibe
- Initiation of lipid or lipoprotein apheresis
- Initiation of oligonucleotide therapy, including antisense oligonucleotides, and siRNA, other than SLN360. Vaccines using mRNA technology are permitted
- Initiation of sex hormone replacement therapy for male or female participants
- Initiation of anti-oestrogen or oestrogen receptor modulator (e.g., tamoxifen)

If during the course of the study, a participant needs additional medication, surgery or an investigation that affects participation in the study or otherwise compromises either the participant's safety or the integrity of the data collected, this should be discussed with the Medical Monitor. The participant may be withdrawn from the study, if deemed necessary, and replaced if appropriate; all participants that have been dosed should complete follow-up assessments even if withdrawn. The participant's treating physician(s) must be informed of the experimental therapy and the likely effects of SLN360 on Lp(a) levels, other plasma lipid fractions and markers of toxicity.

10. PARTICIPANT COMPLETION AND WITHDRAWAL

10.1. Participant Completion

The participant will be classed as having completed the study once they have completed the EoS visit, which will be up to 36 weeks after the last administration of treatment, depending on group, or an early withdrawal visit.

10.2. Participant Withdrawal

10.2.1. Participant Withdrawal of Consent

A participant may withdraw consent for:

- Treatment
- Follow-up visits
- Non-patient contact follow-up, e.g., medical records checks

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal.

Participants requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardise the public health value of the study. Patients who withdraw should also be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

[redacted]

The participant should withdraw consent preferably in writing and, if the participant refuses or is physically unavailable, the site should document and sign the reason for the participant's failure to withdraw consent in writing.

10.2.2. Participant Withdrawal from Study

Participants may withdraw from the study at any time and for any reason without the need for justification. Participants may also be withdrawn by the Investigator if, in the Investigator's opinion, further participation in the study would be deleterious to the participant's health. Reasons for withdrawal could include unacceptable adverse reactions, protocol violation or administrative reasons. To maintain the value and integrity of the study, excessive withdrawals should be avoided where possible.

Where consent remains, every effort must be made to follow-up participants and, other than re-dosing, the scheduled trial assessments should be performed if possible. A reason for withdrawal and an early withdrawal clinic assessments (consisting of assessments included in the Week 36 and EoS visit) as per the Time and Events tables (Appendix 15.1 and Appendix 15.2) are essential.

10.2.3. Participant Withdrawal from Investigational Product

A participant will be withdrawn from treatment for any of the following reasons:

- Withdrawal of consent to continue with treatment. The reason for this will be documented if provided
- Lack of compliance, as assessed per the Investigator and/or the Sponsor
- Adverse events that cannot be tolerated by the participant

The reason(s) for withdrawal must be recorded in the eCRF. If a participant is withdrawn from treatment, every effort must be made for the participant to attend scheduled trial assessments if possible. Where a participant withdrawn from treatment is unable to attend scheduled assessments, every effort must be made to have them return for the Week 36 and EoS visits, if possible. Only if the participant is unable to attend scheduled assessments, follow-up may include contact with managing physicians or pharmacists, medical record review and limited phone call visits.

10.3. Long-term Follow-up

Where participants are lost to follow-up, continued efforts to locate participants during long-term follow-up until the EoS visit will be conducted in accordance with local regulations including available public records to determine vital status.

[redacted]

10.4. Treatment after the End of the Study

Participants will not be provided with study treatment following the end of the study. Regular treatment that participants received before entering the study can be continued following study completion.

10.5. Screening and Baseline Failures

If, after review pre-dose on Day -1 or Day 1, any eligibility criteria are found not to be met, the participant may be rescreened at the Investigator's discretion, or should be deemed a baseline failure. If a patient has a positive SARS-CoV-2 antigen lateral flow test or active coronavirus disease 2019 (COVID-19) infection during screening, rescreening should take place at least 4 weeks after the initial screening.

For participants who do not pass at screening or baseline, at least the ICF, demographics, inclusion and exclusion criteria, reason for screen failure and any AEs during screening will be collected in the eCRF. Information on screening and baseline failures will be collected and may be used for the final analysis.

10.6. Testing for SARS-CoV-2

Testing for SARS-CoV-2 will be completed using an antigen-based point-of-care lateral flow test at each visit. A positive test result should be confirmed with a second test immediately after the first.

In the event of a confirmed positive test result on or shortly before a dosing day, that dose administration should be delayed until the participant has a negative test result and dose administration is deemed clinically appropriate by the Investigator. If the first dose is delayed because of a positive test result, all subsequent visits should also be delayed accordingly. If a second or third dose is delayed because of a positive test result, the impacted visit will be delayed. All subsequent visits should be completed according to their original schedule as described in the Time and Events tables (Appendix 15.1 and Appendix 15.2), i.e., not delayed.

Administration of doses outside the visit windows should not, *per se*, be grounds for withdrawing a participant unless this is deemed clinically appropriate by the Investigator.

A positive SARS-CoV-2 test result should be recorded as an AE, even if the participant is asymptomatic for COVID-19.

[redacted]

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug/ investigational drug in humans, whether or not considered drug related. An AE can therefore be any unfavourable 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.

11.1.2. Adverse Events of Special Interest

An AE of special interest, whether serious or non-serious, is one of scientific and medical concern specific to the Sponsor's study drug/device or programme, which warrants ongoing monitoring and rapid communication by the Investigator to the Sponsor. Such an event might warrant further investigation to characterise and understand it. Adverse events of special interest may include events noted in prior studies. No AEs have been determined, for reporting purposes, to be AEs of special interest in this study.

11.1.3. Serious Adverse Events

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

1. Results in death
2. Is life-threatening

NB: An AE is 'life-threatening' if the patient is at immediate risk of death from the event as it occurs (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 resolves without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis can be fatal.

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

NB: Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical

[redacted]

judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

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 treating physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness 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 centre. This should be recorded in the study file
- Hospitalisation for survey visits or annual physicals fall into the same category
- Hospitalisation is required for an elective intervention of a pre-existing condition that has not worsened from study treatment
- Hospitalisation for social reasons/circumstances

11.1.4. Adverse Drug Reactions

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

Suspected unexpected serious adverse reactions (SUSARs) are SAEs, classed as related, which are not specified as expected in the approved IB. An unexpected adverse drug reaction is defined as an adverse reaction, the nature and severity of which is not consistent with the applicable product information (e.g., the IB for an unapproved IMP).

[redacted]

11.2. Assessment of Adverse Events

11.2.1. Adverse Event Severity

Intensity of all AEs will be graded according to 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 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

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

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

11.2.2. Adverse Event Causality

The Investigator (or appropriately qualified designee) will determine 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 judgement and categorise as detailed in the following sections.

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, or
- It could not readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patients; or it follows a known pattern of response to the test drug

[redacted]

Not Related to Study Treatment

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

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

Adverse events, medical history and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) according to the version specified in the Data Management Plan. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary according to the version specified in the Data Management Plan.

11.2.3. Structured Causality Assessment for Suspected Drug-induced Liver Injury

In the specific case of causality assessment for possible drug-induced liver injury, decision making is based on compatible clinical course, typical changes in hepatic biochemistry and careful, systematic exclusion of all other reasonable causes such as the following: 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 heredity liver diseases (e.g., Wilson's disease), and other hepatotoxic drugs [Aithal *et al*, 2011].

Comprehensive causality assessment for possible drug-induced liver injury should utilise 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 [Regev, 2014].

In all cases, structured causality assessment should consider the following: history and concomitant diseases, temporal relationship with study drug, including latency to time from first drug exposure to qualifying laboratory tests or compatible symptoms, which include the following: increasing fatigue; anorexia; nausea; vomiting; right upper quadrant pain; pattern of injury (hepatocellular, cholestatic, or mixed) based on the first set of laboratory tests that meet the threshold for possible drug-induced liver injury and using the R value; injury severity, including peak values and assessment of hepatic synthetic function (prothrombin time/international normalised ratio and albumin);

washout data, i.e., the resolution and time taken to reach a reduction in serum enzymes to ≥50% peak and 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 [Chalasani *et al*, 2014].

11.3. Safety Reporting

11.3.1. Reporting Adverse Events

All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes or diseases should be noted on the 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 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.

Surgical procedures not prohibited in the eligibility criteria that were planned before 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 patient's medical history.

Each AE is to be documented on the eCRF with reference to the 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 to AEs and resolution dates are to be documented on the eCRF.

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 intensity category changes over time, then those changes should be recorded separately (with distinct onset dates).

11.3.2. Reporting Serious Adverse Events

In the event of an SAE, regardless of suspected causality, the Investigator must notify the Sponsor and/or its safety representative immediately, without undue delay, and under no circumstances later than 24 hours of becoming aware of the event using study specific SAE forms. The Investigator must provide detailed follow-up AE information, as necessary, to the Sponsor and/or its safety representative in a timely manner to meet regulatory reporting requirements. Serious AEs must also be reported to the Independent Ethics Committee/Institutional Review Board according to their policies and procedures.

[redacted]

Recruitment episodes, complications or progression of the initial SAE must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previous reported one should be reported separately as a new event.

If an Investigator becomes aware of an SAE occurring after discontinuation but he or she considers it to be related to study drug, the Investigator should report the event to the Sponsor.

11.4. Follow-up of Adverse Events

For the purposes of this study, the period of observation for collection of AEs extends from the time the patients 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 stabilises at a level acceptable to the Investigator.

Every reasonable effort will be made to follow up with patients who have AEs. Any patient who has an ongoing AE that is related to the IMP 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 stabilised. This will be completed at the Investigator's (or designee's) discretion. Any patient who has an ongoing AE that is not related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the Investigator's and Sponsor's discretion.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilises, returns to randomisation values (if a randomisation value is available) or is shown to not be attributable to the study drug or procedures.

11.5. Pregnancy

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (e.g., postpartum complications, spontaneous miscarriage, still birth, or congenital anomaly [even of an aborted foetus]), the Investigator should follow the procedures for reporting an SAE (Sections 6.5.7 and 11.3.2). Note, elective termination of a pregnancy would not meet the criteria for an SAE, and in these cases, a follow-up pregnancy report should be provided by the Investigator.

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The database will be locked and the main analysis will be performed after all participants have completed 36 weeks of treatment. All follow-up data collected up to Week 60 will be analysed subsequently and included in the final report.

[redacted]

Prior to the database lock (either at main or final analysis), a detailed, finalised Statistical Analysis Plan (SAP) will be completed, approved and placed on file. The SAP will contain a more comprehensive description of the statistical analyses methodology for the study than outlined in this Protocol. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations, database closure and unblinding of the randomisation code. The SAP will also contain the rules and data handling conventions that will be used to perform the analyses and the procedure(s) that will be used to account for missing data. Any change to the analysis methods described in the Protocol will be documented in the SAP and/or Clinical Study Report (CSR) along with the justification for making the change. Additional exploratory analyses performed after the database lock that are not described in the SAP can be conducted as deemed appropriate. These additional analyses will be fully identified as exploratory post-hoc analyses in the CSR.

12.1. Hypotheses

To demonstrate the treatment effect of SLN360 compared with placebo, the following hypothesis:

$$H0: \mu T = \mu P$$

will, at the 5% significance level, be tested against the alternative hypothesis:

$$H1: \mu T > \mu P$$

wherein μ denotes the mean time-averaged change in Lp(a) from baseline to Week 36, T denotes SLN360 and P denotes placebo. For estimating treatment effects, the difference between treatments and corresponding confidence intervals will be provided.

12.2. Estimands

12.2.1. Primary Estimand

The primary estimand for this study is defined by the following attributes:

- Target population: participants with elevated Lp(a) at high risk of ASCVD events
- Treatments: SLN360 versus placebo
- Primary outcome measure: time-averaged change in Lp(a) from baseline to Week 36
- Analysis set and handling of intercurrent events: All available values of Lp(a) will be included in the calculation of time-averaged change from baseline in Lp(a)
- Population level summary: difference in mean time-averaged change in Lp(a) from baseline to Week 36 between treatment groups

[redacted]

Further details will be included in the SAP.

12.2.2. Secondary Estimands

Secondary estimands, if used, will be specified in the SAP.

12.3. Study Design Considerations

12.3.1. Sample Size Assumptions

A total of five treatment groups and approximately 160 participants are planned. Each placebo group will include 20 randomly allocated participants, and each SLN360 group will include 40 randomly allocated participants. This will result in a total of 120 participants exposed to SLN360 and 40 participants exposed to placebo. The placebo groups will be analysed and reported both separately and in combination.

The treatment effect observed in the FIH Phase 1 study (APOLLO; ClinicalTrials.gov identifier NCT04606602; EudraCT identifier 2020-002471-35) between placebo and 300 mg SLN360 at Day 150 (the smallest effect observed at the lowest dose to be used in the proposed study) was approximately 60% with a conservative pooled standard deviation of 40%. As few as 10 participants per arm would give approximately 90% power to detect this magnitude of difference, at the 5% significance level ($p < 0.05$).

The proposed sample size, even separating the placebo arms with a different dose frequency, is expected to be more than adequate to demonstrate the SLN360 effect on Lp(a). The larger sample size should allow a more robust evaluation of safety at these doses and dose frequencies than a smaller sample size that may be expected in a Phase 2 study.

12.3.2. Sample Size Sensitivity

The sensitivity of the sample size will not be investigated because 40 participants per active arm are planned and as few as 10 participants per arm would provide adequate power.

12.3.3. Sample Size Re-estimation

No sample size re-estimation will occur during the study.

12.4. Data Analysis Considerations

Analysis of variance methodology will be used to test for differences between active treatment and placebo for the primary endpoint of time-averaged change from baseline in Lp(a) and secondary endpoints including time-averaged, percent and absolute change

[redacted]

from baseline in Lp(a) and other lipids/lipoproteins including LDL-C, total cholesterol and apoB. Multiplicity adjustment to the type 1 error will be applied for comparisons of active treatment arms versus placebo with similar dosing regimens and will be described in the SAP. Pairwise comparisons between active arms will be considered exploratory and multiplicity adjustments will not be applied.

The distribution of Lp(a) is expected to be positively skewed, but the percentage change from baseline Lp(a) value is not expected to have the same distribution; therefore, parametric testing is appropriate. Testing the assumption of normality will be performed before any formal analysis and sensitivity analyses will be undertaken, if required. Full details of this process will be included in the SAP.

Baseline will be defined as last non-missing observation/measurement before the start of study drug administration.

Descriptive statistics will be used to summarise safety and PD endpoints by treatment group.

Each SLN360 dosing regimen will be presented separately.

12.4.1. Analysis Populations

The following analysis populations will be included for this study:

- Screened Population: all participants who signed an ICF
- Safety Population: all participants who received at least one dose of study drug
- Pharmacodynamic Population: all participants who received at least one dose of study drug and have evaluable PD data

12.4.2. Treatment Comparisons

Treatment comparisons will be made between the active treatment arms and the placebo arms.

12.4.3. Interim Analysis

There will not be a formal interim data analysis. The main analysis will be performed after all participants have completed 36 weeks of treatment. All follow-up data collected up to Week 60 will also be analysed and reported.

[redacted]

12.4.4. Key Elements of Analysis Plan

12.4.4.1. Efficacy Analyses

12.4.4.1.1. Primary endpoint

Analysis of variance methodology will be used to test for differences between active treatment and placebo for time-averaged change in serum Lp(a) for the PD population. Individual and mean and/or median Lp(a) will also be presented graphically as per each scheduled visit by treatment group.

12.4.4.1.2. Secondary endpoints

Pharmacodynamic biomarker data will be listed and summarised using analysis of variance techniques based on the PD Population. Individual and mean and/or median PD biomarkers will also be presented graphically as per each scheduled visit by treatment group.

12.4.4.2. Safety Analyses

Safety and tolerability will be evaluated in the Safety Population by means of AE reports, physical examination findings, 12-lead ECGs, vital signs and laboratory safety evaluations. Safety parameters will be listed and summarised using descriptive statistics. No formal statistical hypothesis testing is planned for safety data.

Descriptive statistics of vital signs, 12-lead ECGs and safety laboratory evaluations at each visit will be presented by treatment group. The changes from baseline will be similarly presented. Physical examination findings will be listed.

12.4.4.2.1. Adverse events

The verbatim terms used in the eCRF by Investigators to identify AEs will be coded using MedDRA. All reported AEs with onset during the treatment phase will be included in the analysis and will be summarised by treatment group, and these include the following: AEs that have worsened since study entry, TEAEs, study drug-related TEAEs, serious TEAEs, study drug-related serious TEAEs, TEAEs leading to study discontinuation, TEAEs leading to discontinuation of study treatment or TEAEs leading to death. All other AEs will be listed only.

For each AE, the number and percentage of participants who experience at least one occurrence of the given event will be summarised by treatment group. Summaries will be presented overall and also by system organ class and preferred term using MedDRA. TEAEs will also be summarised by severity and relationship classified by System Organ Class and Preferred Term.

[redacted]

The number and percentage of early withdrawals and the corresponding reasons will be tabulated presenting number and percentage of participants for each treatment group.

Summaries, listings, datasets or narratives may be provided, as appropriate, for those participants who die, discontinue treatment due to an AE or experience a severe or serious AE.

12.4.5. Missing, Unused and Spurious Data

Missing data will be accounted for in all summaries by time, with reasons provided where possible (e.g., discontinuation). If any data are excluded from analyses, the reason for exclusion will be documented in the CSR.

Imputation of missing data will be described in the SAP.

12.4.6. Reporting Deviations from the Statistical Plan

Any deviations from the planned analyses will be described and justified in the final CSR.

13. STUDY ADMINISTRATION

13.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Before initiation of a study site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the study in accordance with the International Council for Harmonisation – Good Clinical Practice (ICH-GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH-GCP, all applicable participant privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- An Independent Ethics Committee/Institutional Review Board review and approval of study protocol and any subsequent amendments and all ICFs or other information given to the participant
- Participant informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing or both.

[redacted]

Written informed consent must be obtained from each participant before participation in the study, ahead of the pre-screening optional visit and ahead of the screening visit as part of the main study (Section 6.1). Written informed consent will be collected following a review of the participant's information leaflet by the potential participant and a discussion between the participant and the Investigator or suitably qualified designee.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this study. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site(s) by an outside authority before the Inspectors are permitted access to any of the study records or the study areas.

13.2. Study Monitoring

In accordance with applicable regulations, ICH-GCP, the monitoring plan and the Sponsor's and/or delegate procedures, monitors will contact the site before the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The Sponsor and or delegated monitors will perform monitoring during the conduct of the study to ensure that:

- The data are authentic, accurate and complete
- The participant's safety and rights are being protected
- The study is conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP and all applicable regulatory requirements

Taking into account recent limitations with on-site monitoring relating to the COVID-19 pandemic or other restrictions, remote monitoring visits may be performed.

13.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the Medical Monitor, Sponsor-appointed auditors, Sponsor-appointed delegates and regulatory inspectors direct access to all relevant documents.

13.2.2. Data Handling and Record Keeping

Following closure of the study, the Investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must

[redacted]

be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than a hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor's standard operating procedures and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

13.3. Provision of Study Results and Information to Investigators

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR.

The Sponsor will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.

13.4. Data Management

For this study, participant data will be collected using an eCRF and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with the applicable Sponsor or designee standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events, medical history and concomitant procedures will be coded using MedDRA according to the version specified in the Data Management Plan. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary according to the version specified in the Data Management Plan.

[redacted]

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

- Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability and consistent intended performance (i.e., validation)
- Maintain standard operating procedures for using these systems
- Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)
- Maintain a security system that prevents unauthorised access to the data
- Maintain a list of the individuals who are authorised to make data changes
- Maintain adequate backup of the data
- Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)

Training on the use of the electronic data collection system will be provided to all relevant study site staff.

13.5. Insurance, Indemnity and Finance

The Sponsor will maintain appropriate insurance coverage for the clinical studies and follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this study against future claims by study participants; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all study procedures have been carried out according to this protocol.

The financial aspects of the study are addressed in a separate agreement.

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14. REFERENCES

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

Arsenault BJ, Petrides F, Tabet F, Bao W, Hovingh GK, Boekholdt SM, et al. Effect of atorvastatin, cholesterol ester transfer protein inhibition, and diabetes mellitus on circulating proprotein subtilisin kexin type 9 and lipoprotein(a) levels in patients at high cardiovascular risk. J Clin Lipidol. 2018;12(1):130-6.

Berman CL, Barros SA, Galloway SM, Kasper P, Oleson FB, Priestley CC, et al. OSWG Recommendations for Genotoxicity Testing of Novel Oligonucleotide-Based Therapeutics. Nucleic Acid Ther. 2016;26(2):73-85.

Cegla J, Neely RDG, France M, Ferns G, Byrne CD, Halcox J, et al. HEART UK consensus statement on Lipoprotein(a): A call to action [published correction appears in Atherosclerosis. 2020;296:48]. Atherosclerosis. 2019;291:62-70.

Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109(7):950-66; quiz 967.

Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361(26):2518-28.

Emdin CA, Khera AV, Natarajan P, Klarin D, Won HH, Peloso GM, et al. Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels. J Am Coll Cardiol. 2016;68(25):2761-72.

Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412-23.

Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993-2000.

Food and Drug Administration. Guidance for Industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf [accessed 28 April 2022].

[redacted]

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol. 2019 Jun 25;73(24):3234-3237]. J Am Coll Cardiol. 2019;73(24):3168-209.

Helgadottir A, Gretarsdottir S, Thorleifsson G, Holm H, Patel RS, Gudnason T, et al. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol. 2012;60(8):722-9.

Janas MM, Harbison CE, Perry VK, Carito B, Sutherland JE, Vaishnaw AK, et al. The Nonclinical Safety Profile of GalNAc-conjugated RNAi Therapeutics in Subacute Studies. Toxicol Pathol. 2018;46(7):735-45.

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301(22):2331-9.

Koren MJ, Moriarty PM, Baum SJ, Neutel J, Hernandez-Illas M, Weintraub HS, et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). Nat Med. 2022;28(1):96-103.

Larsson SC, Gill D, Mason AM, Jian T, Bäck M, Butterworth AS, et al. Lipoprotein(a) in Alzheimer, Atherosclerotic, Cerebrovascular, Thrombotic, and Valvular Disease: Mendelian Randomization Investigation. Circulation. 2020;141(22):1826-8.

Lim ET, Würtz P, Havulinna AS, Palta P, Tukiainen T, Rehnström K, et al. Distribution and medical impact of loss-of-function variants in the Finnish founder population. PLoS Genet. 2014;10(7):e1004494.

Mehta A, Vasquez N, Ayers CR, Patel J, Hooda A, Khera A, et al. Independent Association of Lipoprotein(a) and Coronary Artery Calcification with Atherosclerotic Cardiovascular Risk. J Am Coll Cardiol. 2022;79(8):757-68.

Nissen SE, Wolski K, Balog C, Swerdlow DI, Scrimgeour AC, Rambaran C, et al. Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals with Elevated Plasma Lipoprotein(a) Levels. JAMA. 2022;327(17):1679-87.

O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation. 2019;139(12):1483-92.

Patel AP, Wang (汪敏先) M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, et al. Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease:

New Insights from a Large National Biobank. Arterioscler Thromb Vasc Biol. 2021;41(1):465-74.

Que X, Hung MY, Yeang C, Gonen A, Prohaska TA, Sun X, et al. Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice [published correction appears in Nature. 2018;561(7724): E43]. Nature. 2018;558(7709):301-6.

Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Seidah NG, et al. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. J Lipid Res. 2016;57(6):1086-96.

Regev A. Drug-induced liver injury and drug development: industry perspective. Semin Liver Dis. 2014;34(2):227-39.

Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1489-99.

Saleheen D, Haycock PC, Zhao W, Rasheed A, Taleb A, Imran A, et al. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis [published correction appears in Lancet Diabetes Endocrinol. 2017 Sep;5(9): e6]. Lancet Diabetes Endocrinol. 2017;5(7):524-33.

Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018;379(22):2097-107.

Szarek M, Bittner VA, Aylward P, Baccara-Dinet M, Bhatt DL, Diaz R, et al. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. Eur Heart J. 2020;41(44):4245-55.

Tsimikas S, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, et al. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. Lancet. 2015;386(10002):1472-83.

Tsimikas S, Fazio S, Ferdinand KC, Ginsberg HN, Koschinsky ML, Marcovina SM, et al. NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. J Am Coll Cardiol. 2018;71(2):177-92.

Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, et al. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. N Engl J Med. 2020;382(3):244-55.

[redacted]

Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet Lond Engl. 2016;388(10057):2239-53.

Zheng KH, Tsimikas S, Pawade T, Kroon J, Jenkins WSA, Doris MK, et al. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients with Aortic Stenosis. J Am Coll Cardiol. 2019;73(17):2150-62.

15. APPENDICES PROVIDED FOR STUDY SLN360-002

15.1. Appendix: Time and Events Table – Groups 1 and 3 (Dosing Every 16 Weeks)

Procedure	Optional Pre-screening	Screening	Intervention Period											Follow-up Period		EoS
Week	-6	-4	0	1	4	8	12	16	20	24	28	32	36	40	48	60
Day	-	-	1	8	29	57	85	113	141	169	197	225	252	281	337	421
Window (days)	-		-	-	±1	±2	±3	±3	±4	±6	±7	±8	±9	±10	±12	±14
Informed consent	X	X														
Eligibility assessment	X[a]	X														
Viral serology		X														
Demography		X														
Medical history		X														
Lifestyle and dietary restrictions		X	X					X				X				
Physical examination[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant/ prior medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation			X													
Dose administration			X					X				X				
SARS-CoV-2 testing[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Optional Pre-screening	Screening	Intervention Period											Follow-up Period		EoS
Week	-6	-4	0	1	4	8	12	16	20	24	28	32	36	40	48	60
Day	-	-	1	8	29	57	85	113	141	169	197	225	252	281	337	421
Window (days)	-		-	-	±1	±2	±3	±3	±4	±6	±7	±8	±9	±10	±12	±14
Pregnancy testing[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reaction assessment			X	X				X	X			X	X			X
12-lead ECG[e]		X	X	X	X			X				X				X
Safety lab markers (blood)[f]		X	X	X	X	X	X	X		X		X		X		X
Urinalysis		X	X	X	X			X				X				X
PD markers[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genotyping sample			X													
Anti-drug antibody assessment sample			X		X			X				X	X			X
AE recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; ECG=electrocardiogram; EoS=end-of-study; Lp(a)=lipoprotein(a); PD=pharmacodynamic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

a. Limited eligibility assessment to be conducted at the optional pre-screening visit
b. A full physical examination is required at screening, pre-dose on Day 1 and EoS. An abbreviated physical examination is to be conducted at visits thereafter if indicated by symptoms, signs or other findings
c. A SARS-CoV-2 antigen lateral flow test will be conducted pre-dose on each dosing day and at all other visits
d. A serum pregnancy test is required at screening. Urine pregnancy testing will be performed at other timepoints
e. On dosing days, vital signs should be performed pre-dose and at 5 minutes and 1 hour post-dose

[redacted]

Procedure	Optional Pre-screening	Screening	Intervention Period											Follow-up Period		EoS
Week	-6	-4	0	1	4	8	12	16	20	24	28	32	36	40	48	60
Day	-	-	1	8	29	57	85	113	141	169	197	225	252	281	337	421
Window (days)	-		-	-	±1	±2	±3	±3	±4	±6	±7	±8	±9	±10	±12	±14

f. On dosing days, 12-lead ECG should be performed pre- and 1 hour (+/- 30mins) post-dose.
g. A list of safety laboratory parameters is presented in Section 6.5.6. Note that the full set of parameters listed may not be assessed at every timepoint
h. On dosing days, blood samples for PD biomarkers should be collected pre-dose. Note that the full set of parameters listed in Section 6.4 may not be assessed at every timepoint. If an optional pre-screening visit is conducted only Lp(a) is to be measured at that visit

Note: Participants may stay at sites overnight on the night before and/or after a visit if required.

[redacted]

15.2. Appendix: Time and Events Table – Groups 2, 4 and 5 (Dosing Every 24 Weeks)

Procedure	Optional Pre-screening	Screening	Intervention Period											Follow-up Period		EoS
Week	-6	-4	0	1	4	8	12	16	20	24	28	32	36	40	48	60
Day	-	-	1	8	29	57	85	113	141	169	197	225	252	281	337	421
Window (days)	-		-	-	±1	±2	±3	±3	±4	±6	±7	±8	±9	±10	±12	±14
Informed consent	X	X														
Eligibility assessment	X[a]	X														
Viral serology		X														
Demography		X														
Medical history		X														
Lifestyle & dietary restrictions		X	X							X						
Physical examination[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant/ prior medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation			X													
Dose administration			X							X						
SARS-CoV-2 testing[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Procedure	Optional Pre-screening	Screening	Intervention Period											Follow-up Period		EoS
Week	-6	-4	0	1	4	8	12	16	20	24	28	32	36	40	48	60
Day	-	-	1	8	29	57	85	113	141	169	197	225	252	281	337	421
Window (days)	-		-	-	±1	±2	±3	±3	±4	±6	±7	±8	±9	±10	±12	±14
ISR assessment			X	X						X	X					X
12-lead ECG[e]		X	X	X	X					X	X					X
Safety lab markers (blood)[f]		X	X	X	X	X	X	X		X		X		X		X
Urinalysis		X	X	X	X					X		X				X
PD markers[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genotyping sample			X													
Anti-drug antibody assessment sample			X		X					X	X					X
AE recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; ECG=electrocardiogram; EoS=end-of-study; ISR=injection site reaction; Lp(a)=lipoprotein(a); PD=pharmacodynamic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

a. Limited eligibility assessment to be conducted at the optional pre-screening visit
b. A full physical examination is required at screening, pre-dose on Day 1 and EoS. An abbreviated physical examination is to be conducted at visits thereafter if indicated by symptoms, signs or other findings
c. A SARS-CoV-2 antigen lateral flow test will be conducted pre-dose on each dosing day and at all other visits
d. A serum pregnancy test is required at screening. Urine pregnancy testing will be performed at other timepoints
e. On dosing days, vital signs should be performed pre-dose and at 5 minutes and 1 hour post-dose
f. On dosing days, 12-lead ECG should be performed pre- and 1 hour (+/- 30mins) post-dose.
g. A list of safety laboratory parameters is presented in Section 6.5.6. Note that the full set of parameters listed may not be assessed at every timepoint

[redacted]

Procedure	Optional Pre-screening	Screening	Intervention Period											Follow-up Period		EoS
Week	-6	-4	0	1	4	8	12	16	20	24	28	32	36	40	48	60
Day	-	-	1	8	29	57	85	113	141	169	197	225	252	281	337	421
Window (days)	-		-	-	±1	±2	±3	±3	±4	±6	±7	±8	±9	±10	±12	±14

h. On dosing days, blood samples for PD biomarkers should be collected pre-dose. Note that the full set of parameters listed in Section 6.4 may not be assessed at every timepoint. If an optional pre-screening visit is conducted only Lp(a) is to be measured at that visit

Note: Participants may stay at sites overnight on the night before and/or after a visit if required.

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15.3. Appendix: Study Reports – Internal

DD-0001: Schubert S. *In vitro* screening of siRNA sequences for inhibition of LPA mRNA expression in a human cell line and in primary hepatocytes. Silence Therapeutics GmbH, Berlin, Germany. February 2020.

DD-0004: Eisermann M. Measurement of PLG Messenger RNA in samples originating from Covance Study Number 8387516 “A 9-week Study on the Pharmacodynamic Effects and Safety of Subcutaneous GalNAc-siRNA Administration in Cynomolgus Monkeys”. Silence Therapeutics GmbH, Berlin, Germany. February 2020.

LYO-X-2022-06-0003: Wade J. Pharmacokinetics and pharmacodynamics of SLN360 in the Phase 1 single ascending dose study and PK/PD simulations to support Phase 2 dosing selection. Silence Therapeutics GmbH, Berlin, Germany. June 2022.

15.4. Appendix: Study Reports – External

STEPS-0069: Schefchek J. A 9-week Study on the Pharmacodynamic Effects and Safety of Subcutaneous GalNAc-siRNA Administration in Cynomolgus Monkeys. Covance Laboratories Inc., Madison, WI, USA. May 2019.

STEPS-0099: McPhie G. 22-week Pharmacokinetic/Pharmacodynamic Study of SLN360 Following Subcutaneous Administration to the Male Cynomolgus Monkey. Covance Laboratories Ltd, Harrogate, UK. May 2020.

STEPS-0100: Pressl J. Development of anti-X0619-specific antibodies in rabbit BioGenes GmbH, Berlin, Germany. September 2019.

STEPS-0105: Gibson L. SLN360: 29-day Subcutaneous Administration Toxicity Study in the Rat Followed by an 8 Week Recovery Period. Covance Laboratories Ltd, Harrogate, UK. December 2020.

STEPS-0106: McPhie G. SLN360: 29-day Subcutaneous Administration Toxicity Study in the Monkey Followed by an 8-week Recovery Period. Covance Laboratories Ltd, Harrogate, UK. December 2020.

STEPS-0118: Hargreaves V. SLN360: *In Vitro* L5178Y Gene Mutation Assay at the tk locus. Covance Laboratories Ltd, Harrogate, UK. May 2020.

STEPS-0119: Hargreaves V. SLN360: *In Vitro* Human Lymphocyte Micronucleus Assay. Covance Laboratories Ltd, Harrogate, UK. June 2020.

STEPS-0120: Luo G. *In Vitro* Plasma Protein Binding of SLN360 in Rat, Monkey and Human. Covance Laboratories Inc., Madison, WI, USA. March 2020.

STEPS-0121: Luo G. Metabolism of SLN360 in Rat, Monkey, and Human Hepatic Postmitochondrial Supernatant Fractions (S9). Covance Laboratories Inc., Madison, WI, USA. February 2020.

STEPS-0122: Luo G. Metabolism of SLN360 in Monkey and Human Hepatic Lysosomes. Covance Laboratories Inc., Madison, WI, USA. March 2020.

STEPS-0124: Campbell R. SLN360: Cytochrome P450 Induction in Cultured Human Hepatocytes. Sekisui XenoTech, LLC, Kansas City, KS, USA. April 2020.

STEPS-0125: Snyder R. SLN360: Cytochrome P450 Inhibition in Suspended and Cultured Cryopreserved Human Hepatocytes. Sekisui XenoTech, LLC, Kansas City, KS, USA. May 2020.

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STEPS-0126: Takare R. SLN360: ABC and SLC Transport in Cells. Sekisui XenoTech, LLC, Kansas City, KS, USA. May 2020.

STEPS-0128: Niehoff M. SLN360: 13-week Subcutaneous Administration Toxicity Study with a 13-Week Recovery Period in Sexually Mature Cynomolgus Monkeys. LabCorp Muenster, Münster, Germany. March 2022.

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