STATISTICAL ANALYSIS PLAN

Protocol Title:	A randomized, double-blind, placebo controlled, first-in-human study to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic response of SLN360 in subjects with elevated lipoprotein(a)
Protocol Number:	SLN360-001
Protocol Version/Date:	Version 6.0/ 09 November 2021
Investigational Product:	SLN360
Sponsor:	Silence Therapeutics plc 72 Hammersmith Road London W14 8TH UK
SAP Version/Date:	SAP V4.0/ 20 September 2023

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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Nick Allison
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VERSION HISTORY

Version	Version Date	Description
1.0	23 December 2021	Original signed version
2.0	25 May 2023	- New analysis population added (Pharmacodynamic Per Protocol (PDPP) Population) to account for patients in the MD part of the study who were not administered a second dose – sections 3.2.4, 3.5 and 6 revised. - PK analysis for MD Cohorts clarified (section 3.4).
3.0	08 September 2023	- Reference to Baseline 2 removed (all change from baseline summaries will be relative to the first dose of the study drug). - Injection site erythema/redness and induration/swelling change from baseline summary removed.
4.0	20 September 2023	- Updates to PD, PK, and safety lab data handling rules.

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TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
apoB	Apolipoprotein B
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to infinite time
$AUC_{0-tlast}$	Area under the plasma concentration-time curve from time 0 to the last quantifiable plasma concentration
AUC_{tau}	AUC from dosing time to dosing time (Tau - dosing interval) (MD only)
BDRM	Blinded Data Review Meeting
BLQ	Below the Limit of Quantitation
CL/F	Apparent total plasma clearance
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed plasma concentration
eCRF	Electronic case report form
CSR	Clinical Study Report
DLT	Dose-limiting toxicity
EoS	End of study visit
HDL-C	High density lipoprotein cholesterol
IRT	Interactive response technology
LDL-C	Low density lipoprotein cholesterol
Lp	Lipoprotein
MD	Multiple doses
MedDRA	Medical Dictionary for Regulatory Activities
OxPL	Oxidized phospholipid
PD	Pharmacodynamics
PK	Pharmacokinetics
Q4W	every 4 weeks
Q8W	every 8 weeks
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SDTM	Study Data Tabulation Model
SRC	Safety Review Committee
$t_{½}$	Apparent elimination half-life
Tau	The dosing interval
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum observed drug concentration
λz	Apparent terminal elimination rate constant
Vz/F	Apparent volume of distribution
WHO	World Health Organization

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1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number SLN360-001. The SAP will be finalized prior to database lock of corresponding single ascending dose (SAD) or multiple dose (MD) part. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is:

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

2.1.2 Efficacy Objective

i. Pharmacodynamic (PD) effects of single and multiple doses of SLN360 on Lp(a) (assessment of Lp(a) will be considered the primary evaluation of efficacy).

2.1.3 Secondary Objectives

The secondary objectives include assessment of the following:

i. Pharmacokinetics (PK) of SLN360 after a single and multiple dose administration.

ii. Extent and duration of reduction in Lp(a) following single and multiple doses of SLN360.

iii. Impact of dose schedule of SLN360 on extent and duration of reduction in Lp(a).

2.1.4 Exploratory Objectives

The exploratory objectives include assessment of the following:

i. Impact of single and multiple doses of SLN360 on lipid profile including apolipoprotein B (apoB), oxidized phospholipid (OxPLs), inflammatory markers and plasminogen.

2.2 Study Design

2.2.1 Overview

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

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

For each cohort, safety and, where available, PK data will be reviewed and assessed by the Safety Review Committee (SRC) before recommending progression to the next dose escalation.

The study design is summarized in Figure 1.

Figure 1:SLN360-001 Study Design Overview

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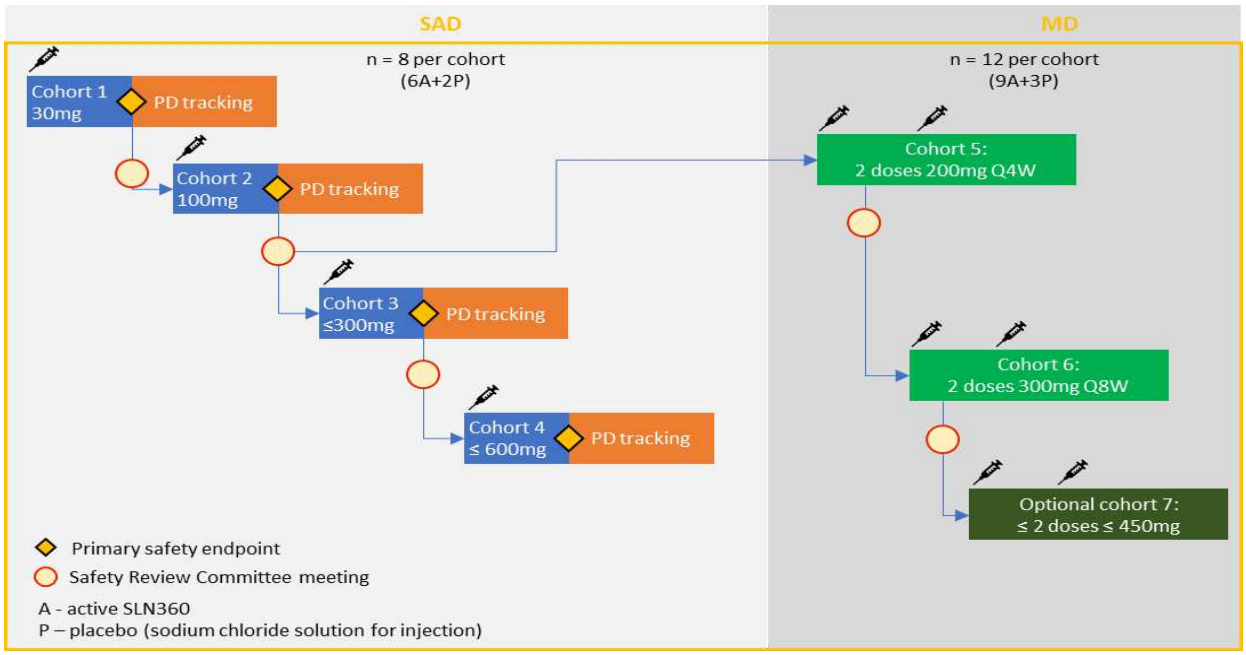

SAD Part

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

MD Part

Up to three cohorts, each consisting of 12 subjects (9 active: 3 placebo) with elevated Lp(a) levels will be treated with doses and at dose frequencies of SLN360 informed by data from the SAD part. Subjects will be admitted as inpatients for dosing and at least 24 hours of post-dose monitoring and assessment. Subjects will be followed for up to 201 days (duration informed by data from SAD) from the first dose to understand the magnitude and durability of the Lp(a) response to multiple dose administration of SLN360. As for the SAD cohorts, the PD effect of SLN360 will be evaluated by measuring plasma levels of Lp(a) and a range of other lipid fractions (LDL-C, HDL-C, total cholesterol, triglyceride, and apoB). PK parameters will also be assessed at several timepoints after dosing. The final dose levels and dosing frequency of the MD cohorts will be dependent on safety, tolerability, PD and PK findings from the SAD part of the study. The SRC may recommend increasing the duration of follow-up beyond the currently planned 201 days up to a maximum of 365 days.

The dose level in each cohort for the MD part of the study will be recommended by the SRC based on the safety, PD and PK data from the SAD part of the study. Each dose of SLN360 administered during this part of the study will not exceed the maximum dose level studied in the SAD part of the study. Up to two doses

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will be administered in each cohort in the MD part. The interval between the first and second doses in each MD cohort will be determined on the recommendation of the SRC based on available safety, tolerability, PK and PD data from the SAD part. The second dose will be administered no sooner than 4 weeks after the first dose. The maximum dose level administered in each MD cohort will not be greater than that administered during the SAD part.

2.2.2 Dose Escalation

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

The recommendation to introduce the MD part of the study will be made by the SRC no sooner than 4 weeks after all subjects within the 100 mg SAD cohort receiving SLN360 have completed 90 days of follow-up. The planned doses and regimens are shown in Table 1.

Table 1: Dose escalation levels

	Cohort (dose)	**Dose level description**	**Minimum no. of SLN360-treated subjects for SRC assessment**
SAD part:	1 (30 mg)	1/10 of expected therapeutic dose	4
	2 (10 0mg)	Lower limit of expected therapeutic dose	4
	3 (≤ 300 mg)	Expected therapeutic dose	4
	4 (≤ 600 mg)	Upper limit of expected therapeutic dose	4
MD part:	5 (2x ≤ 200 mg Q4W)	-	6
	6 (2x ≤ 300 mg Q8W)	-	6
	7 (≤ 2x ≤ 450 mg)*	Optional additional dose	6

Note: Dose and dosing interval in the MD part to be confirmed based on SAD findings.

*Optional cohort 7 may be used to evaluate either multiple or single dosing. The relevant Schedule of Assessments will be used depending on whether multiple or single dosing is employed.

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2.2.3 Randomization and Blinding

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

The Investigators, subjects, Sponsor and delegated site members will be blinded to study drug, and the site pharmacist(s) and person administering the drug will be unblinded.

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

During the course of the study, the SRC will review blinded data in open sessions but will have access to the treatment assignment, if required, during closed sessions.

2.2.4 Study Drug

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

Placebo treatment (commercial sodium chloride injection, 0.9% w/v administered via s.c. injection) will be provided by the Sponsor (or designee) and stored in accordance with the conditions specified on the label.

Each dose of SLN360 or placebo will be administered as s.c. injection(s) by appropriately qualified clinical study site staff. For analysis purposes, a dose is used to refer to the entire drug administered per visit, rather than an individual injection. The preferred site for all injection(s) is the abdomen, avoiding areas where the skin is red, bruised, tender, hard or in sites of previous scars. Where other medicinal products are required to be given by s.c. administration, these should preferably be administered at different sites.

Individual injection volume at each injection site will not exceed 1.5 mL, and up to 3 injection sites may be used to achieve the required dose.

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

In the SAD part of the study subjects will receive the dose on day 1. In the MD part of the study, subjects are planned to receive a first dose on Day 1 and second dose no earlier than Day 28. Optional cohort 7 may evaluate either single or multiple doses; in the latter case the second dose should be administered no earlier than day 28. In the SAD part of the study, the 4 planned dose levels (cohorts) to be tested are 30, 100, 300 and 600 mg. The SRC may also request an additional/intermediate dose in the SAD part of the study. The dose and inter-dose interval for the MD part of the study will be selected based on the safety, PD and PK data from the SAD part of the study.

2.2.5 Sample Size Determination

Four cohorts of eight subjects (with each consisting of 6 active: 2 placebo) are planned in the SAD part resulting in 24 subjects being exposed to SLN360 and 8 subjects being exposed to placebo (cohorts 1–4).

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

Two cohorts of 12 subjects (each consisting of 9 active: 3 placebo) are planned in the MD part resulting in 18 subjects being exposed to SLN360 and 6 subjects being exposed to placebo (cohorts 5–7). An additional optional cohort of 12 subjects (9 active: 3 placebo) may be evaluated if recommended by the SRC (cohort 7). Thus, in the MD part of the study, a total of up to 27 subjects will be exposed to SLN360 in up to 3 cohorts, and a total of up to 9 subjects will be exposed to placebo treatment.

Of the total number of subjects planned for enrolment in the trial, including the optional cohort, up to a maximum of 51 evaluable subjects will be exposed to SLN360, and up to a maximum of 17 evaluable individuals will be exposed to placebo over the course of the study.

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary objective is to determine the safety and tolerability of SLN360. The following safety and tolerability endpoints will be evaluated:

- Treatment emergent AEs (TEAEs), including injection site reactions; severity and causality will be evaluated
- DLTs assessed by TEAEs that meet the DLT criteria
- Safety laboratory results including chemistry, hematology, coagulation parameters, and urinalysis
- Vital signs
- Physical examinations
- ECGs

2.3.2 Secondary Endpoints

The secondary endpoints will be included:

- Pharmacodynamic effects of SLN360: measuring plasma levels of Lp(a) and a range of other lipid fractions (LDL-C, HDL-C, total cholesterol, triglyceride).
- Pharmacokinetic parameters of SLN360, including maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), time of the maximum observed plasma concentration (t_{max}), apparent plasma terminal elimination half-life ($t_{1/2}$), apparent total plasma clearance (CL/F), apparent volume of distribution (Vz/F) after single and multiple administrations.
- Change from baseline in Lp(a) following single and multiple doses of SLN360 to assess extent and duration of reduction in Lp(a).

2.3.3 Exploratory Endpoints

Change from baseline of single and multiple doses of SLN360 on lipid profile including apoB, OxPLs, inflammatory markers and plasminogen.

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3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

No study visit window will be used for analyses. Analysis visits will be based on the nominal visits as captured on the eCRFs.

3.1.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug.

3.1.4 Summary Statistics

SAD and MD parts of the study will be reported separately.

Subjects assigned to placebo from each SAD cohort will be pooled to create an overall placebo treatment group. SLN360 treatment groups will be presented separately by dose and combined across all SLN360 doses for summary of AEs and injection site reactions.

Descriptive statistics will be used to summarize safety, PD and PK endpoints by treatment group. For categorical variables, summary tabulations of frequency and percentage of subjects within each category will be presented with 95% confidence intervals, where appropriate. For continuous variables, the number of subjects, mean, median, 25th and 75th percentiles, standard deviation, minimum, and maximum values with 95% confidence intervals, where appropriate, will be presented by treatment group.

For PK plasma SLN360 concentration, descriptive statistics will also include coefficient of variation (CV %), geometric mean (GM) and GM CV (%).

3.1.5 Hypothesis Testing

No formal statistical testing will be carried out.

3.1.6 Evaluation of Site Effect

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.1.7 Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified. Only observed data will be used in the summaries and analyses.

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE is missing / incomplete, it is assumed to have occurred during the active phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

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3) If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e. an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date.).

4) Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

3.2 Analysis Populations

3.2.1 Screened Population

The Screened Population is defined as all subjects who signed the informed consent form.

3.2.2 Safety Population

The Safety Population is defined as all subjects who received at least 1 dose of study drug.

3.2.3 Pharmacodynamic (PD) Population

The PD Population is defined as all subjects who received at least 1 dose of study drug and have evaluable PD data (i.e. baseline and at least one post-baseline value).

3.2.4 Pharmacodynamic Per Protocol (PDPP) Population

The PDPP Population is defined as all subjects enrolled in the MD part of the study who received 2 doses of study drug at 2 different visits and have evaluable PD data (a dose is used to refer to the entire drug administered per visit, rather than an individual injection).

3.2.5 Pharmacokinetic (PK) Population

The PK Population is defined as all subjects who received at least 1 dose of study drug and have evaluable PK data (i.e. at least 3 measurable post-dose concentrations).

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition and Analysis Populations

Subject disposition, including numbers of subjects who were screened and randomized will be summarized. Numbers and percentage of subjects completed, as well as those discontinued with the detail of the reasons for discontinuation, will also be summarized. Numbers and percentage of subjects in each analysis population will be tabulated by treatment group and overall. Reasons for exclusion from each analysis population, as well as reasons for screen failure will also be summarized.

3.3.2 Protocol Deviations

Protocol deviations will be identified according to the Protocol Deviation Plan. Counts and percentages of subjects with protocol deviations by deviation category and protocol deviations due to COVID-19-related reasons will be summarized by treatment group and overall based on the Screened Population.

3.3.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (18-64 years, ≥65 years)

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- Sex (male, female)
- Childbearing potential (yes, no)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported, unknown)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Alcohol use (yes, no)
- Recreational drug use (yes, no)
- Time from the initial date of elevated Lp(a) to the informed consent date (months)

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

3.3.4 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment group and overall based on the Safety Population.

3.3.5 Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version Mar 2020G B3. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has a missing start date, the most conservative approach will be applied and the medication start date will be assumed to be during the active phase unless other data (e.g. stop date) indicates differently. For a missing stop date, the medication will be assumed to be ongoing.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and overall based on the Safety Population.

As COVID-19 vaccinations are being introduced during the course of this study, depending on the type of vaccine and the number of subjects vaccinated, additional analyses might be required. This will be assessed at the time of the BDRM.

Concomitant procedures will be coded to system organ class and preferred term using MedDRA version 23.0 and listed.

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3.3.6 Study Treatment

For the SAD, total dose administered (mg), total planned and actual volume administered (mL), whether full dose was administered plus reason for not administering the full dose and number of injections will be summarized by treatment based on the Safety Population with descriptive statistics.

For the MD part, total dose administered (mg), total planned and actual volume administered (mL), number of doses and duration of exposure will be included in an overall summary by treatment based on the Safety Population with descriptive statistics.

Duration = Date of last injection- Date of first injection +1.

For each dose, whether full dose was administered plus reason for not administering the full dose and number of injections will be summarized by treatment based on the Safety Population with descriptive statistics.

All information collected on the eCRF related to study treatment will be listed.

3.4 Pharmacokinetic Assessment

For SAD, samples for the PK assessment will be collected on Days 1, 2 and 7. For MD, samples for the PK assessment will be collected in cohort 5 on Days 1, 2, 3, 7, 14, 30, 31, 32, 36, 43, 60 and 90; in cohort 6 on Days 1, 2, 3, 7, 14, 30, 60, 61, 62, 66, 73, 90 and 120. In optional MD cohort 7, the timing of PK samples will be determined by the final dosing schedule selected for that cohort. On dosing days in the SAD cohorts, samples will be collected at the following time points: pre-dose and 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours post-dose and 30-36 hours post-dose; in the MD cohorts samples will be collected at the following time points: pre-dose and 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 9 hours, 12 hours, 18 hours and 24 hours post-dose.

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

3.4.1 Handling Missing Data or Concentration Below the Lower Limit of Quantification

If the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged and the scheduled time point may be used for the calculation of PK parameters.

In cases of missing pre-dose on Day 1, the missing components will be assumed as zero. For the other cases, the missing data will not be imputed.

The following rules will be used to handle BLQ for the PK parameter calculation and individual concentration data:

- If one or more BLQ values occur before the first measurable concentration (including dose #1 predose), they will be assigned as zero concentration.
- If BLQ values occur between measurable concentrations, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

The following general rules will be applied for the concentration summary (including tabulation and plotting):

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- Descriptive statistics for concentrations at any individual time point will only be calculated if at least half of the subjects have valid values (i.e. quantifiable and not missing) at this time point.
- In cases where descriptive statistics are not calculated, due to the above criterion not being met, the mean value will be set to missing for mean plotting purposes.
- If BLQ values occur between measurable concentrations, the BLQ should be omitted (set to missing).
- All other BLQs will be set to zero for the calculation of descriptive statistics.

3.4.2 Pharmacokinetic Concentrations

Individual and mean SLN360 concentration-time profiles will also be presented graphically. Mean (±SD) concentration will be plotted on linear and semi logarithmic scales against nominal time points by treatment group, when available.

Plasma concentrations of SLN360 will be listed and summarized using descriptive statistics based on PK Population by treatment group. Individual plasma concentrations will also be listed for the PK Population.

Actual sampling times will be used in the calculation of PK parameters and individual concentration plotting but times that are outside the sampling time windows will be reviewed at the BDRM to confirm any exclusions from concentration summary and mean concentration plotting.

The acceptable windows are as follows:

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

3.4.3 Pharmacokinetic Parameters

Plasma PK parameters of SLN360 will be determined using non-compartmental analysis and the following PK parameters will be determined, as appropriate, from the plasma concentrations of SLN360 after a single dose (Day 1) and multiple doses (Day 1 and Day 30 or Day 60):

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Parameters	Description
C_{max}	maximum observed drug concentration
C_{last}	last observed drug concentration
t_{max}	time to maximum observed drug concentration; if the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value
λ_z	apparent terminal elimination rate constant
$t_{½}$	apparent elimination half-life; calculated as $\ln(2)/\lambda_z$
$AUC_{0\text{-}tlast}$	area under the plasma concentration-time curve (AUC) calculated using linear-up log-down trapezoidal summation from time 0 to the last quantifiable plasma concentration (C_{last})
$AUC_{0\text{-}24}$	AUC from time 0 to 24 hours
AUC_{tau}	AUC from dosing time to dosing time (Tau - dosing interval) (MD only)
$AUC_{0\text{-}\infty}$	AUC from time 0 to infinity
$AUC_{\%extrap}$	Percent of AUC0-∞ extrapolated; calculated as $(1 - AUC_{0\text{-}tlast} / AUC_{0\text{-}\infty})*100$ (SAD and MD Day 1 only)
CL/F	apparent clearance; calculated as $Dose/AUC_{0\text{-}\infty}$ (SAD and MD Day 1 only)
V_z/F	apparent volume of distribution; calculated as $Dose/ [\lambda_z * AUC_{0\text{-}\infty}]$ (SAD and MD Day 1 only)

Actual collection times will be used in PK parameter calculations. The Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values. In order to estimate the apparent first-order terminal elimination constant, λ_z, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points post C_{max}. Uniform weighting will be selected to perform the regression analysis to estimate λ_z. The constant λ_z will not be assigned if one of the following occurs:

- the terminal elimination phase is not linear (as it appears on a semi-logarithmic scale)
- the terminal elimination rate constant indicates a positive slope ($\lambda_z > 0$)
- t_{max} is one of the 3 last data points
- the adjusted regression coefficient (R^2) is less than 0.8

In cases where the λ_z interval is not assigned, the values of associated parameters (eg. λ_z, $t_{½}$, $AUC_{0\text{-}\infty}$) will not be calculated. If $AUC_{\%extrap}$ is greater than 20%, the related PK parameters will be excluded from the summary but flagged in the appropriate listing.

PK parameters will be listed and summarized by treatment group using descriptive statistics for the Pharmacokinetic Population.

3.4.4 Exploratory Dose Proportionality

If feasible, exploratory dose proportionality will be analyzed for SAD and MD day 1 using power model based on Pharmacokinetic Population as appropriate. The power model is described below as:

$$y = \alpha \times Dose^{\beta}$$

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where y denotes the plasma PK parameters ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}). The exponent, β, in the power model will be estimated by regressing the ln transformed PK parameter on ln transformed dose. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. Given the small sample size for each dose level, this exploratory dose proportionality analysis will estimate the mean slope and the corresponding 90% confidence interval (CI) will be calculated.

The PK data will be reviewed by the unblinded pharmacologist before final study unblinding, including a check that results are within a logical order over time when plotted. Specific data values will be considered invalid and may be excluded from the PK data analysis after clinical and blinded review of the data if they meet any of the following criteria:

- Any PK sample value collected following confirmed incorrect/opposite study medication administration (specifically administration of medication assigned to a different cohort or arm than randomized).
- Non-BLQ values at pre-dose before first dose of IMP administration or following documented incorrect study medication administration.
- Pre-dose PK sample collected after the respective dosing event of the PK profile.
- Measurable PK sample values in the placebo group.

Documentation of excluded/spurious PK values will be finalized before MD database lock.

3.5 Pharmacodynamic Assessment

Samples for the PD assessment will be collected at every scheduled visit (with the exception of Screening for MD). On dosing days samples will be collected at the following time points: pre-dose and 6, 12, and 24 hours post-dose. PD biomarkers will include Lp(a), apoB, LDL-C, HDL-C, total cholesterol, triglycerides, OxPLs, high sensitivity C-reactive protein, interleukin-6 and plasminogen.

Any BLQ observations in PD data (if applicable) will be imputed as LLOQ/2 except for baseline which will be treated as zero.

Biomarker data will be summarized using descriptive statistics based on the PD population for the SAD part of the study, and the PDPP Population for the MD part of the study. Mean and/or median PD biomarkers (dependent on the distribution of the data) will also be presented graphically against scheduled visit by treatment group based on the PD population for the SAD part of the study, and the PDPP Population for the MD part of the study. The median plots for the SAD part will be produced as an ad hoc analysis.

Number and percentage of patients with Lp(a) ≤50mg/dl (125nmol/liter) at scheduled visit will be provided by treatment group, also based on the PD population for the SAD part of the study, and the PDPP Population for the MD part of the study.

Individual biomarker data will be listed, and individual biomarkers will also be presented graphically against scheduled visit by treatment group, both based on the PD Population.

No formal statistical analysis of PD data is planned.

All PD data will be reviewed by the unblinded pharmacologist before final study unblinding, including a check that results are within a logical order over time when plotted. Specific data values will be considered invalid and may be excluded from the PD data analysis after clinical and blinded review of the data if they meet the following criteria:

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- Any PD sample value collected following confirmed incorrect/opposite study medication administration (specifically administration of medication assigned to a different cohort or arm than randomized).

Documentation of excluded/spurious PD values will be finalized before MD database lock.

3.6 Safety Assessment

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the Safety Population.

3.6.1 Adverse Events (AEs)

All AEs will be coded to system organ class and preferred term using MedDRA version 23.0. Treatment emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) on a five-point scale (Grade 1 to 5). Study drug-related AEs are defined as AEs considered by the investigator as having a reasonable possibility of being related to study drug.

An overview of TEAEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug-related TEAEs (overall and by maximum severity)
- Any AESIs
- Any SAEs
- Any serious TEAEs
- Any study drug-related serious TEAEs
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any TEAEs leading to death

An AE of special interest (AESI) (serious or nonserious) is an AE of greater scientific and medical concerns specific to study drug. AESIs include the following:

- AEs that potentially meet dose-limiting toxicity (DLT) criteria
- Injection site reactions

Summary tables of TEAEs, study drug-related TEAEs, AESIs, serious TEAEs and TEAEs leading to discontinuation of study drug or study will be provided with the number and percentage of subjects with adverse events and the number of events classified by primary system organ class, and preferred term. System organ classes and preferred terms will be sorted alphabetically.

For tabulations that include classification by relationship to study drug, TEAEs with missing relationship will be considered related to study drug. For tabulations that include classification by severity, missing severity will be considered as the most severe TEAEs that are not SAEs.

Adverse event listings will be presented by subject, system organ class and preferred term.

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3.6.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected at every scheduled visit and processed by a central laboratory. On dosing days samples will be collected at the following time points: pre-dose and, 6, 12, and 24 hours post-dose. A list of laboratory tests to be performed is specified in the protocol.

Values and changes from baseline will be presented at each scheduled visit and baseline by laboratory test.

Shift tables from baseline to scheduled post-baseline will be tabulated for all laboratory parameters, if applicable.

The number and percentage of subjects with the following potentially clinically significant abnormal liver function tests will be summarized:

- ALT >3xULN, >5xULN, >10xULN, and >20xULN
- AST >3xULN, >5xULN, >10xULN, and >20xULN
- ALP ≥2xULN
- Total bilirubin >2xULN
- ALT or AST ≥3×ULN with total bilirubin >2×ULN
- INR >1.5
- ALT or AST ≥3xULN with INR>1.5

Both scheduled and unscheduled results will be considered in clinical laboratory tables.

Listings will list results in Standard International units and conventional units and sort by test, date and time.

Lab values will be checked to ensure no values are reported which could not be in accordance with a patient's symptoms or safety. Any lab measurement confirmed as invalid, including marked as 'GROSS HEMOLYSIS', 'INTERFERENCE', 'QUESTIONABLE INTEGRITY', may be excluded from analysis, following clinical and blinded review of data. Documentation of excluded/spurious lab values will be finalized before MD database lock.

3.6.3 Vital Signs

Vital signs will be measured at each scheduled visit. On dosing days vital signs will be measured at the following time points: pre-dose and 1, 6, 12, and 24 hours post-dose.

Vital signs will include systolic and diastolic blood pressure, heart rate, body temperature and respiratory rate. Descriptive statistics will be provided for vital sign values as well as change from baseline at each scheduled visit.

3.6.4 12-lead Electrocardiograms

For SAD, ECGs will be performed at Screening and on Days 1, 7, 14, 30, 60, 90, and 150. Additionally, ECGs will be performed on Day 365 for cohorts 3 and 4. For MD, ECGs will be performed at each scheduled visit except day prior to dosing, 2 and 3 days post-dose. On dosing days ECGs will be performed at the following time points: pre-dose and 1, 6, 12, and 24 hours post-dose.

For the continuous variables, descriptive statistics of results at each study visit, as well as the change from baseline to each study visit, will be presented in summary tables; for the categorical responses to overall

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interpretation (rhythm), results and the associated findings at each visit will be summarized by counts and percentages.

Number and percentage of patients with QTcF interval in the categories below will be provided.

- Absolute QTcF interval >500 msec,
- Absolute QT interval >500 msec,
- Increase from baseline QTcF interval >60 msec.

A shift table from baseline to scheduled post-baseline will be tabulated for overall interpretation (rhythm).

All the data collected will be listed.

3.6.5 Injection Site Assessments

For SAD, assessments for injection site reactions will be performed on Days 1 and 7. For MD, assessments will be performed up to 30 days post-dosing. On dosing days assessments will be performed at the following time points: pre-dose, 30 minutes post-dose, and 1, 2, 6, 12, and 24 hours post-dose.

Pain, tenderness, erythema/redness, and induration/swelling will be graded on a scale from 1 to 3.

The number and percentage of subjects will be presented by graded scale for each of injection site location at each visit and time point.

Values will be presented at each scheduled visit and timepoint by injection site location for erythema/redness and induration/swelling measurements.

Injection site reactions will also be graded as AEs using the NCI-CTCAE 5-point scale (see section 3.6.1).

3.6.6 Physical Examinations

A listing of physical examination assessments will be provided.

3.6.7 Other Safety Assessments

Pregnancy test, COVID-19 test, Drug Induced Liver Injury and recreational drug and alcohol use will be listed.

4 SAFETY REVIEW COMMITTEE

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

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

The decision to proceed to the next dose escalation of the study will be made by the Sponsor on the recommendation of the SRC.

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5 ANALYSIS TIMING

5.1 Interim Analysis

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

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The statistical analysis plan introduced the following modifications to the analyses planned in the protocol:

1. The protocol section 7.6 stated that safety and tolerability were to be evaluated by means of DLTs (SAD cohorts only). DLTs will also be analyzed for MD part.
2. On the recommendation of the SRC, the SAD optional cohort (cohort 4a) was not opened. As this was prior to SAP finalization, all references to cohort 4a have been removed from the SAP.
3. The text “Up to two doses will be administered in each cohort in the MD part” in SAP section 2.2.1 MD part differs from protocol section 2.7, to clarify that optional cohort 7 may be used to evaluate either multiple or single dosing.
4. To clarify the efficacy objective, the objectives as stated in section 2 of the protocol, have been separated into primary, efficacy, secondary and exploratory objectives in SAP section 2.1.
5. New analysis population added (Pharmacodynamic Per Protocol (PDPP) Population) to account for patients in the MD part of the study who were not administered a second dose.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. SDTM programming will follow SDTM version 1.4 together with SDTM implementation guide 3.2. Detailed Programming Specifications will be provided in a separate document.

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