APPENDIX 16.1.9: DOCUMENTATION OF STATISTICAL METHODS

Study Official 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

NCT Number: NCT05537571

STATISTICAL ANALYSIS PLAN

Protocol 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.
Protocol Number:	SLN360-002
Protocol Version/Date:	1.0/09AUG2022
Investigational Product:	SLN360
Sponsor:	Silence Therapeutics plc 72 Hammersmith Road London W14 8TH UK
SAP Version/Date:	2.0/14 February 2024

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SIGNATURE PAGE

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Protocol Number:	SLN360-002
SAP Version/Date:	2.0/ 14 February 2024

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

Signature	Date
[redacted]	14-Feb-2024
	14-Feb-2024
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	14FEB2024

VERSION HISTORY

Version	Version Date	Description
1.0	16SEP2022	Original signed version
2.0	14FEB2024	Section 2.1 clarifications of study primary and secondary objectives Section 2.3 clarifications of primary endpoint and secondary pharmacodynamic and efficacy endpoints Section 3.1 laboratory values imputation rules above and below limits of quantification Section 3.2 Pharmacodynamic Per-Protocol (PDPP) Population is removed. Section 3.4 clarifications of time-averaged AUC calculation excluding Day 1 pre-dose value and using actual time instead of nominal time Section 3.4 clarifications of using pooled group in analysis of variance analysis

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ASCVD	atherosclerotic cardiovascular disease
apoB	apolipoprotein B
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	area under the curve
BMI	Body mass index
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical Study Report
ECG	Electrocardiogram
FIH	First-in-human
HDL-C	High-density lipoprotein cholesterol
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IRT	interactive response technology
LDL-C	low-density lipoprotein cholesterol
LLQ	Lower limit of quantification
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Pharmacodynamics
Q16W	Dosing every 16 weeks
Q24W	Dosing every 24 weeks
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
ULQ	Upper limit of quantification
WHO	World Health Organization

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 SLN360-002. The SAP will be finalized prior to database lock and unblinding. 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 to evaluate the effect of SLN360 on circulating molar concentration of lipoprotein(a) (Lp(a)) in participants with elevated Lp(a) at high risk of ASCVD events.

2.1.2 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
- Evaluate the effects of SLN360 on Lp(a) mass concentration, apolipoprotein B (apoB), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides in this population

2.1.3 Exploratory Objective

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

2.2 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 atherosclerotic cardiovascular disease (ASCVD).

2.2.1 Overview

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)

2.2.2 Randomization 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.

2.2.3 Study Drug

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). 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.

Dose groups and treatment regimens are summarised in Table 1.

Table 1 Dose groups and treatment regimens for the proposed Phase 2 study

Group	Regimen	No. of doses of SLN360	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

2.2.4 Sample Size Determination

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 first-in-human (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.

2.3 Study Endpoints

2.3.1 Primary Endpoint

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

2.3.2 Secondary Endpoints

2.3.2.1 Safety

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

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

2.3.2.2 Pharmacodynamics and Efficacy

The secondary pharmacodynamic (PD) and efficacy endpoints are:

- Time-averaged percent change in Lp(a) molar concentration from baseline to Week 48 and Week 60.
- Time-averaged absolute change in Lp(a) molar concentration from baseline to Week 36, Week 48, and Week 60.
- Time-averaged percent and absolute change in Lp(a) mass concentration, ApoB, LDL-C, HDL-C, total cholesterol and triglycerides, from baseline to Week 36, Week 48, and Week 60.
- Percent and absolute change in Lp(a) molar concentration, Lp(a) mass concentration, ApoB, LDL-C, HDL-C, total cholesterol, triglycerides, oxidized phospholipids, and C-reactive protein, from baseline by visit (i.e., not time-averaged)

2.3.3 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).

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

For pharmacodynamics and efficacy parameters, visits will be assigned to analysis visits according to the following visit windows. Within each analysis visit window, scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). If no scheduled visit is within the analysis visit window, measurement(s) taken at a visit close to the target analysis day will be used as the measurement for that specific visit. Unscheduled visits will not be used unless the scheduled result has not been reported. If samples are collected after the scheduled week 60 analysis these will not be included.

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Screening			
Baseline	1		1
Week 1	8	2	19
Week 4	29	20	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	238
Week 36	252	239	267
Week 40	281	268	309
Week 48	337	310	379
Week 60	421	380	

No study visit window will be used for safety parameters. Analysis visits will be based on the nominal visits as captured on the CRFs.

3.1.3 Definition of Baseline

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

3.1.4 Laboratory Values Above or Below Limits of Quantification

For laboratory values less than the lower limit of quantification (LLQ), half of the lower limit value (i.e., LLQ/2) will be used in the efficacy analyses described below. Likewise, for values greater than the upper limit of quantification (ULQ), the upper limit value (i.e., ULQ) will be used in the efficacy analyses.

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, 25th and 75th percentiles, standard deviation, minimum, maximum and 95% confidence intervals where appropriate.

3.1.6 Hypothesis Testing

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

H_0: $\mu_T = \mu_P$

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

H_1: $\mu_T > \mu_P$

wherein μ denotes the mean time-averaged change in Lp(a) from Day 1 pre-dose 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.

No formal statistical hypothesis testing is planned for safety data.

3.1.7 Evaluation of Site Effect

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

3.1.8 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.
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

Screened Population includes all participants who signed an informed consent form (ICF).

3.2.2 Safety Population

Safety Population includes all participants who received at least one dose of study drug.

3.2.3 Pharmacodynamic Population

Pharmacodynamic Population includes all participants who received at least one dose of study drug and have evaluable PD data.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened subjects. Reasons for early discontinuation will also be summarized.

Counts and percentages of subjects who were randomized, discontinued treatment early, completed study treatment, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized subjects. Primary reasons for early discontinuation treatment and study will also be summarized. Early discontinuation treatment and study due to Coronavirus disease 2019 (COVID-19) will be summarized.

3.3.2 *Protocol Deviations*

Counts and percentages of subjects with protocol deviations by deviation category will be summarized by treatment and in total based on all randomized subjects. Protocol deviations related to COVID-19 will be summarized in the same manner.

3.3.3 *Analysis Populations*

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects. Reasons for exclusion from each analysis population will also be summarized.

3.3.4 *Demographic and Baseline Characteristics*

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (18-64 years, ≥65 years)
- 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)
- Time from the initial date of elevated Lp(a) to randomization date (months)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for the Safety Population.

3.3.5 *Medical History*

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

Counts and percentages of subjects with high-risk conditions for ASCVD will be summarized by treatment and in total based on the Safety Population.

3.3.6 *Concomitant Medications*

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary. 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 summarised by treatment and in total based on the Safety Population.

3.3.7 Study Drug Exposure and Compliance

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 (weeks) = (Date of last injection- Date of first injection +1))/7.

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 Efficacy Assessment

Efficacy data will be summarized by randomized treatment based on Pharmacodynamic Population.

3.4.1 Primary Endpoint

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 percent change in Lp(a) molar concentration from Day 1 pre-dose to Week 36
- Analysis population: Pharmacodynamic Population
- Intercurrent events: prohibited medications/procedures and permitted medications (defined in protocol section 9.2 and 9.3), death, early withdrawal from study drug, and early withdrawal from the study.
- Analysis set and handling of intercurrent events: Treatment policy strategy will be used. All values of Lp(a) from scheduled assessments up to Week 36 will be included in the calculation of time-averaged percent change for each participant
- Population level summary: difference in mean time-averaged percent change in Lp(a) from Day 1 pre-dose to Week 36 between treatment groups

Time-averaged percent change from Week 4 to Week 36 is calculated from Week 4 corrected area under the curve (AUC) using linear trapezoidal method from Week 4 to Week 36 divided by the per-patient total time interval. Note that the Day 1 pre -dose values will be excluded from the time-averaged calculations (i.e., for each participant, the initial value included in the calculation will be from their first scheduled post-baseline assessment). Furthermore, the actual analysis day of each assessment will be used in the AUC calculation.

If the last available measurement of Lp(a) is before Week 36, time-averaged percent change in Lp(a) from Day 1 pre-dose to Week 36 will be calculated by arithmetic mean of all percent changes in Lp(a) from Day 1 pre-dose up to the last available time point before Week 36.

Analysis of variance will be used to test for differences between each active treatment group (i.e., Group 3, 4, or 5 in Table 1) and the pooled placebo groups (i.e., Groups 1 and 2 in Table 1 combined) for time-averaged percent change in Lp(a). Time-averaged percent change from Day 1 pre-dose to Week 36 in Lp(a) will be the dependent variable and treatment will be included as a factor. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the pairwise comparisons between the SLN360 and placebo groups will be provided.

Holm's procedure will be used to control multiplicity of pairwise comparisons between each SLN360 group and the pooled placebo group. p-values will be first ordered from the smallest to the largest. $p_{(1)}$ represents the smallest value, $p_{(2)}$ the next-smallest p-value, $p_{(3)}$ the third-smallest p-value.

(1) The test begins by comparing the smallest p-value, $p_{(1)}$, to 0.05/3 or 0.0167. If this $p_{(1)}$ is less than 0.0167, the pairwise treatment comparison with this p-value is considered significant.
(2) The test then compares the next-smallest p-value, $p_{(2)}$, to 0.05/2 or 0.025. If this $p_{(2)}$ is less than 0.025, the pairwise treatment comparison with this p-value is also considered significant.
(3) The test then compares the next ordered p-value, $p_{(3)}$, to 0.05. If this $p_{(3)}$ is less than 0.05, the pairwise treatment comparison with this p-value is also considered significant.

Pairwise comparisons between SLN360 groups will be provided and considered exploratory and multiplicity adjustments will not be applied.

P-values below 0.05 will still be considered nominally significant.

3.4.2 Secondary Pharmacodynamics and Efficacy Endpoints

Time averaged secondary endpoints will be calculated and analyzed using the same conventions as the primary endpoint.

For each PD parameter, percent and absolute change from Day 1 pre-dose to each visit will be summarized descriptively. The least squares means, standard errors, and 2-sided 95% confidence intervals from analysis of variance will be provided for each treatment group and for the pairwise comparisons of each SLN360 group and placebo. Figures displaying mean (+/- standard deviation) by visit will be plotted for Lp(a), Apolipoprotein B, LDL Cholesterol, HDL Cholesterol, Total Cholesterol, Triglycerides, Oxidized Phospholipids, and C Reactive Protein will be displayed at baseline and each post-baseline visit. Additionally, figures for mean change and percent change (+/- standard deviation) from baseline will be presented for Lp(a), Apolipoprotein B, LDL Cholesterol, and C Reactive Protein will be displayed for each post-baseline visit.

3.4.3 Exploratory Endpoints

Analysis of exploratory endpoints, 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), will be described in a separate analysis plan.

3.4.4 Subgroups

There is no planned subgroup analysis.

3.5 Safety Assessment

All safety data will be included in the subject data listings. Safety data will be summarised by actual treatment received (and in total for selected analyses) based on the Safety Population.

3.5.1 Adverse Events (AEs)

All AEs will be coded to system organ class and preferred term using MedDRA. 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 serious adverse events (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

Summary tables of TEAEs, TEAEs by maximum severity, study drug-related TEAEs, 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.

3.5.2 Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be collected at every scheduled visit and processed by a central laboratory. Urine samples will be analysed locally using a dipstick but may also be analysed centrally if indicated and deemed appropriate by the Investigator. 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
- AST >3xULN
- ALP ≥2xULN
- Total bilirubin >2xULN
- ALT or AST ≥3×ULN with total bilirubin >2×ULN

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

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

3.5.3 Vital Signs

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

3.5.4 Electrocardiograms

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 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).

3.5.5 Injection Site Assessments

The number and percentage of subjects will be presented for any pain, tenderness, erythema/redness, and induration/swelling of injection site location at each visit and time point.

3.5.6 Physical Examinations

A listing of physical examination assessments will be provided.

3.5.7 Other Safety Assessments

All other safety assessments will be listed.

4 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.

5 INTERIM ANALYSIS

There will not be a formal interim data analysis. The database will be locked and the primary analysis will be performed after all participants have completed 36 weeks of treatment. Similar analysis will also be performed after all participants have completed 48 weeks of treatment (end of treatment period). All follow-up data collected up to Week 60 will also be analysed and reported (final analysis).

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There are no changes from the protocol-specified statistical analyses.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.