Official Title: A Randomized, Double-Blind, Placebo-controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

NCT Number: NCT02527343

Document Date: SAP Version 2 - June 19, 2019

9. DOCUMENTATION OF STATISTICAL METHODS

The following statistical analysis plan is included:

- Statistical Analysis Plan, ISIS 304801-CS17, Version 2.0 dated 19 June 2019

Sponsor:

Akcea Therapeutics, Inc.

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Boston, MA 02210

Collaborator:

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

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Statistical Analysis Plan

ISIS 304801–CS17

The BROADEN Study

A Randomized, Double-Blind, Placebo-controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

Date: June 19, 2019

Version: 2.0

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Akcea Therapeutics, Inc.

22 Boston Wharf Road, 9th Floor, Boston, MA 02210

Compound Name: ISIS 304801

Protocol: ISIS 304801–CS17

Study Title: A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

Protocol Issue Date: Amendment 4 – August 22, 2017

Signature: [redacted] Date: 6/21/2019

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Akcea Therapeutics, Inc.

PAREXEL SIGNATURE PAGE

This document has been signed electronically on the final page by the following:

	Signatory
Author	[redacted] Project Role [redacted]

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SUMMARY OF CHANGES

Version 2.0 – Added new derived FPL Group based on criteria stated in Section 2.2. In the secondary endpoint, added analysis of change from baseline for hepatic fat fraction and HbA1C. Also included a subgroup analysis of change from baseline for fasting triglycerides, hepatic fat fraction, and HbA1c by genetic mutation status LMNA + PPARG, or no mutation.

ABBREVIATIONS

AE	Adverse Event
ADA	Anti-drug Antibody
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
[redacted]	[redacted]
[redacted]	[redacted]
apoC-III	Apolipoprotein C-III
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
ET	Early Termination
FAS	Full Analysis Set
[redacted]	[redacted]
FPL	Familial Partial Lipodystrophy
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-apoC-III	High-Density Lipoprotein-Apolipoprotein C-III
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
[redacted]	[redacted]
ICH	International Council on Harmonisation

IM	Immunogenicity
INR	International Normalized Ratio
ISR	Injection Site Reaction
IxRS	Interactive Voice/Web-Response System
LCR	Local Cutaneous Reaction
LCRIS	Local Cutaneous Reaction at the Injection Site
LDL-C	Low-Density Lipoprotein Cholesterol
MACE	Major Acute Cardiovascular Event
MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
OLE	Open-Label Extension
PD	Pharmacodynamics
PK	Pharmacokinetics
PPSR	Per Protocol Set in the Randomized Treatment Period
PPSO	Per Protocol Set in the Open-Label Extension
PRO	Patient-Reported Outcomes
PT	Prothrombin Time
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SMBG	Self-Monitoring of Blood Glucose
SSR	Safety Set in Randomized treatment period
SSO	Safety Set in Open-label extension period
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
TG	Triglyceride(s)
ULN	Upper Limit of Normal
[redacted]	[redacted]
VLDL-apoC-III	Very Low-Density Lipoprotein-Apolipoprotein C-III
[redacted]	[redacted]

1 INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the Ionis Pharmaceuticals, Inc. study with Protocol Number ISIS 304801-CS17 (Amendment 4 – 22 August 2017). Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; and, Section 3 provides the detailed plan for the statistical analyses.

Any deviations from the final version of this Statistical Analysis Plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

1.1 Study Overview

Volanesorsen (ISIS 304801) has been evaluated in one Phase 1 study and two Phase 2 studies, all double-blinded and placebo-controlled. The total exposures in completed studies comprise 99 patients and healthy volunteers administered volanesorsen at doses ranging from 50 to 400 mg, administered subcutaneously for up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apolipoprotein C-III (apoC-III) and triglyceride (TG) (~80% and 70%, respectively, mean reduction from Baseline with 300 mg dose once weekly) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background of stable fibrate therapy, patients with Familial Chylomicronemia Syndrome (FCS), and patients with type 2 diabetes mellitus (T2DM).

There has been no clinical or laboratory evidence of drug-drug interactions.

This is a multi-center, randomized, double blind, placebo-controlled study with an open-label extension.

The study will comprise the following periods:

- Screening. An up to 6-week Screening Period, including at least a 4-week diet stabilization phase.
- Randomized Treatment Period. Following the diet-stabilization, up to 70 eligible patients will be randomized 1:1 to receive volanesorsen or placebo once-weekly for 52 weeks.
    - Patients will be stratified by assignment into 1 of 3 groups based on Familial Partial Lipodystrophy (FPL) phenotype, genetic variants and family history of PL. (Minor criteria refers to protocol section 5.1 inclusion criteria)

    1. Group 1 will consist of patients with the FPL phenotype and genetic variants of FPL
    2. Group 2 will consist of patients with the FPL phenotype, but lacking a genetic variant, and having a confirmed family history of FPL or abnormal and similar fat distribution, plus 1 minor criterion

3. Group 3 will consist of those with the FPL phenotype, but without either a genetic variant or family history, plus 2 minor criteria and a BMI < 35 kg/m^2

- Randomized Treatment Post-Treatment Follow-up. Patients who do not enter the OLE period will go straight to the 13-week post-treatment follow-up period.
- An Open-Label Extension (OLE) Year 1 Period. After completion of the 52-week randomized treatment period patients will enter the OLE period and will receive volanesorsen for 52 weeks. Assessments and study visits will be generally similar to the randomized treatment period.
- OLE Year 2 Period. Following the Week 52 visit of the OLE period, patients will have the option of continuing dosing for up to an additional 52 weeks, for a total of up to 2 years (104 weeks) of open label dosing following the 1 year (52 weeks) randomized phase. The schedule of procedures will follow the same schedule as the first year of the OLE.
- A 13-week Post-treatment Evaluation Period. Patients who do not enter the option for additional dosing in the OLE post-treatment period will go straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks or after discontinuing treatment during the first 52 weeks of the OLE. Patients who enter the OLE post-treatment period will go straight to a 13-week post-treatment follow-up period after completion of the Week 104 OLE or after discontinuing treatment prior to Week 104 of the OLE.

The primary endpoint for the study will be evaluated after the last patient has completed the Week 52/ET (Early Termination) visit of the Randomized Treatment Period and will be based on the percent change from Baseline in fasting triglyceride at the primary analysis time point (Month 3).

1.2 Objectives

1.2.1 Primary Objective

To evaluate the efficacy of volanesorsen for reduction in severity of metabolic derangement in patients with Familial Partial Lipodystrophy (FPL) with hypertriglyceridemia and uncontrolled diabetes.

1.2.2 Secondary Objectives

To evaluate the safety and tolerability of volanesorsen in patients with FPL.

To further evaluate the role of serum triglyceride in modulating insulin resistance in FPL patients and the impact of triglyceride reduction on adipose tissue distribution.

1.3 Hypotheses

The study hypothesis is that volanesorsen can significantly reduce the severity of metabolic derangement and is well-tolerated for patients with FPL with hypertriglyceridemia and uncontrolled diabetes.

The hypotheses for primary endpoint at the primary analysis time point are:

- Null hypothesis: volanesorsen and placebo have the same percent change from Baseline in fasting triglyceride to Month 3
- Alternative hypothesis: volanesorsen and placebo have significantly different percent changes from Baseline in fasting triglyceride to Month 3

1.4 Endpoints

The primary analysis time point is at the end of Month 3 where the value is defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting lipid assessments

The Month 6 analysis time point is at the end of Month 6 where the values defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting lipid assessments

The Month 12 analysis time point is at the end of Month 12 where the values defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting lipid assessments.

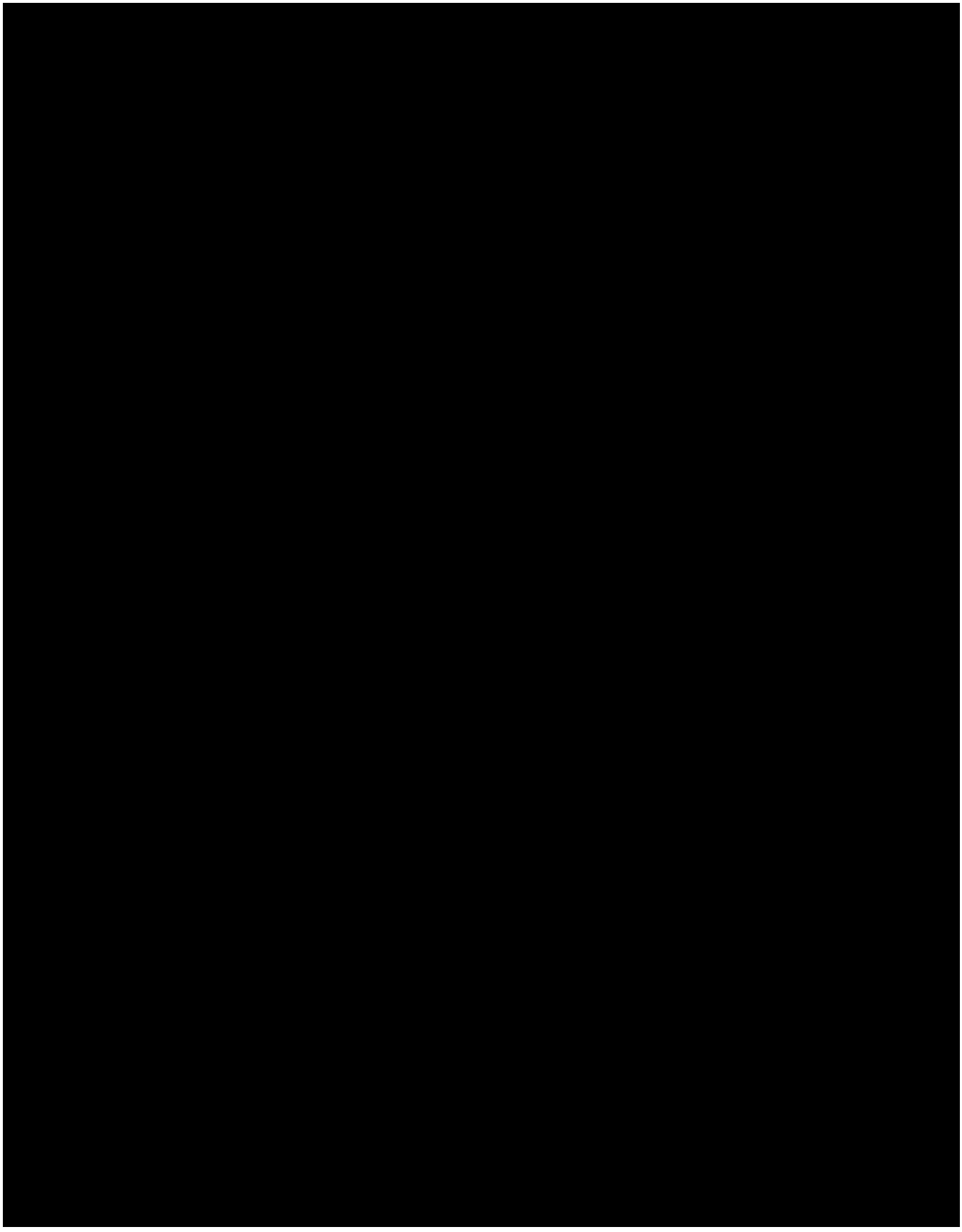
1.4.1 Primary Endpoints

The primary efficacy analysis will be the comparison of percent changes from Baseline to the primary analysis time point in fasting triglyceride between volanesorsen group and placebo group in the Full Analysis Set (FAS).

1.4.2 Secondary Endpoints

The secondary endpoints include:

- Percent change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI])
- The comparison of percent changes from Baseline to the analysis time point in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI]) between treatment groups
- Change from Baseline in hemoglobin A1c (HbA1c)
- The comparison of changes from Baseline to the analysis time point in hemoglobin A1c (HbA1c) between treatment groups
- A composite endpoint at Month 6 for percent of patients who achieve
  a. $\geq$ 40% reduction in fasting triglyceride , and
  b. $\geq$ 30% reduction of hepatic fat fraction percent
- Change in patient-reported outcomes (PRO)
  - Patient-reported pain
  - Patient-reported hunger
  - Quality of life (QOL) questionnaires (EQ-5D, SF-36)



1.4.4 Safety Endpoints

- AEs including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiogram (ECG)
- Use of concomitant medications
- Magnetic Resonance Imaging (MRI)

The details on the safety analyses are discussed in the section 3.7.

2 PROCEDURES

2.1 General Overview of Procedures

2.1.1 Screening and Baseline

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. A 6-week period, including a diet stabilization period of at least 4 weeks, is given to perform the screening evaluations. The baseline assessments will be performed at Week -2 to -1, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes.

2.1.2 Randomized Treatment Period

During the randomized treatment period, patients will report to the study center for clinic visits a minimum of 6 times during Weeks 1-52 (see Schedule of Procedures in Protocol Appendix A). Study Drug will be administered once-weekly (Protocol Section 8.1). Collection and measurement of vital signs, physical examination results, [redacted], ECGs, liver MRIs, echocardiograms, clinical laboratory parameters (including hematology; serum chemistry; lipid panel; [redacted], and CRP measured by high sensitivity assay [hsCRP]; urinalysis, and other analytes listed in Protocol Appendix B), volanesorsen plasma trough concentrations, anti-drug antibody (ADA) testing, [redacted], collection of SMBG and insulin diary, hunger diary, pain diary, and AEs, concomitant medication/procedure information, and QOL assessments will be performed according to the schedule of procedures in Protocol Appendix A. AEs at the injection site should be collected as AEs. Dietary/alcohol counseling will commence at the start of the diet stabilization period and will be reinforced at intervals throughout the treatment and follow-up period.

Patients must be fasted prior to drawing all lipid samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Blood sampling at Weeks 2, 3, 4, 5, 6, 7, 8, 9,

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51 may be conducted by a home healthcare service. While allowed, it is preferable that visits at Week 8 and 12 are conducted at the clinic if possible. Dosing instructions and training will be provided to the patient where applicable.

All visits have a visit window of at least ± 2 days. All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A of the protocol. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

2.1.3 Randomized Period Post-Treatment Follow-Up

Patients who do not enter the OLE period will go straight to the 13-week post-treatment follow-up period. This period consists of 7 visits, as outlined in the Schedule of Procedures in Appendix A of the protocol.

2.1.4 OLE Period

After completion of the 52-week randomized treatment period patients will enter the OLE period and will receive volanesorsen for an additional 52 weeks. Assessments and study visits will be generally similar to the randomized treatment period as outlined in the Schedule of Procedures in Protocol Appendix A, with the inclusion of weekly platelet monitoring.

Following 52 weeks of treatment in the Open-Label Extension Period, patients will have the option of continuing dosing for up to an additional 52 weeks. The schedule of procedures will follow the same schedule as the first year of OLE.

2.1.5 OLE Post-Treatment Period

Following the Week 52 visit of the Open-Label Extension Period, patients will have the option of continuing dosing for up to an additional 52 weeks (second OLE period). Patients who do not enter this option for additional dosing in the OLE period will go straight to the 13-week OLE post-treatment period after completion of the first 52 weeks or after discontinuing treatment during the first 52 weeks of OLE. This period consists of 7 visits, as outlined in the Schedule of Procedures in Protocol Appendix A.

For patients who continue to receive investigational treatment for the second OLE period, the 13-week OLE post-treatment period will follow completion of the Week 156 visit or after early treatment discontinuation.

2.2 Randomization and Treatment Allocation

Patients will be randomized after all screening and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in the protocol sections 5.1 and 5.2. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Using an Interactive Voice/Web-Response System (IxRS), eligible patients will be randomized 1:1 to receive volanesorsen or placebo.

Patients will be stratified by assignment into 1 of 3 groups based on FPL phenotype, genetic variants and family history of PL. (Minor criteria refers to protocol section 5.1 inclusion criteria)

FPL Groups for Stratification

1. Group 1 will consist of patients with the FPL phenotype and genetic variants of FPL.
2. Group 2 will consist of patients with the FPL phenotype, but lacking a genetic variant, and having a confirmed family history of FPL or abnormal and similar fat distribution, plus 1 minor criterion.
3. Group 3 will consist of those with the FPL phenotype, but without either a genetic variant or family history, plus 2 minor criteria and a BMI < 35 kg/m^2.

Genetic analysis reports include characterization of variants into 5 classifications: benign, likely benign, variant of unknown significance, likely pathogenic or pathogenic.

For stratification purposes:

Positive on genetic testing: Documentation of pathogenic or likely pathogenic genes associated with familial partial lipodystrophy will be considered positive for genetic analysis if these changes are likely to represent the underlying cause of the subject's phenotype. This should be documented in a written report.

Negative on genetic testing: When sequencing analysis of the partial lipodystrophy panel for variants determines that no pathogenic or likely pathogenic variant were identified or is a variant of unknown significance, this will be considered as evidence for negative for genetics. Negative on genetics will also be considered for those subjects for whom the genetic analysis results are unlikely, unknown, or untested.

Positive family history of FPL or family history of abnormal and similar fat distribution includes immediate family / first degree relatives (father, mother, brother, sister, daughter, son), as well as second degree relatives (grandparents, aunts and uncles, nieces and nephews, and grandchildren).

A permuted block schedule will be used. The Sponsor Quality Assurance department or designee will hold a copy of the randomization lists generated by the IxRS vendor.

Patients who withdraw from the study will not be replaced.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Agency (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

The Sponsor (or designee) is responsible for processing all reported adverse events (AEs). Processing of serious adverse events (SAEs) is delegated to a CRO although the Sponsor remains accountable for this activity and process. AEs and SAEs are reviewed according to standard operating procedures. The Sponsor medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. The Sponsor (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, the Sponsor (or designee) will also prepare a safety notification letter and transmit it to all applicable study sites.

2.4.2 Data Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter.

In order to ensure maintenance of the study blind, lipid panel results, including apoC-III, will not be available to the Sponsor, monitors, Investigators, Study Center personnel, or the patients, except for the procedure related to safety monitoring for LDL-C elevations as specified in protocol section 8.5.6.

For the purpose of pre-programming and data cleaning, Parexel unblinded programming team (the CRO performing the statistical analysis) and an independent data manager at [redacted] Laboratories will receive post-baseline lipid panel results.

Appendix A lists what data will be included in the DSMB.

2.5 Data Management

2.5.1 Case Report Form (CRF) Data

Bioclinica® is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by the Sponsor (or designee). The Sponsor (or designee) is responsible for the review, data management querying, and locking of the database.

Data are single-entered into the EDC system by the Investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. The Sponsor performs blinded review of all data for accuracy and validity; generating additional queries in the EDC system, when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data is entered, reviewed, source data verified, and after all queries are resolved, the database will be locked.

2.5.2 Laboratory Data

The Sponsor is responsible for the format of the laboratory electronic data transfers and the transfer schedule. The Sponsor (or designee) is responsible for the review of the clinical laboratory data. Central lab data is not stored in the EDC system. Investigator sites have access to this data via printed lab reports sent directly from the laboratory. MRL manages the Central lab data.

2.5.3 Pharmacokinetics (PK) and Anti-drug Antibody (ADA) Data

The Sponsor is responsible for the management and review of the PK and IM data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK and IM data are not stored in the EDC system.

2.5.4 Other Data

[redacted] Central Lab manages MRI/ECHO/[redacted]. Both data will also not be stored in the EDC system but will be transferred to Ionis Pharmaceuticals, Inc. as external data.

2.5.5 Adverse Events Adjudication

SOCAR is the vendor that manages the adjudication process. All SAEs that occur during the study that are consistent with MACE will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter. In addition, this committee will also adjudicate the data for episodes of MACE over the last 3 years prior to randomization, collected by review of each patient's medical chart. All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter.

The adjudication data will be transferred electronically using EXCEL file from SOCAR to Ionis Pharmaceuticals, Inc.

3 ANALYSIS PLAN

3.1 Statistical Design Summary

This is a multi-center, randomized, double blind, placebo-controlled study with an open-label extension comprised of study periods outlined in Section 1.1.

The primary efficacy measurement is fasting triglyceride which will be collected at baseline and all post-baseline visits. The primary analysis model will be a parametric analysis model for percent change in triglyceride from Baseline to Randomized Treatment Period Month 3 by treatment group. As study treatment is discontinued before completing the protocol specified treatment period, missing data imputation and various sensitivity analyses defined by protocol will not be conducted.

The primary endpoint for the study will be evaluated after the last patient has completed the Week 52/early termination (ET) visit and will be based on the percent change from Baseline in fasting TG at the primary analysis time point (Month 3). The Study Team will be unblinded after the last patient's Week 52/ET visit is completed and database is locked.

3.2 General Overview of Analyses

3.2.1 Statistical Methods

All eCRF(Electronic Case Report Form) data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients randomized into the study. Descriptive summary statistics including n, mean, median, standard error, standard deviation, interquartile range (25th percentile, 75th percentile), range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type 1 error rates unless otherwise stated.

Summary of primary efficacy endpoint will only include the on-treatment assessment. On-treatment assessment is defined as assessment since first dose date, up to 28 days after last dose of study medication. Assessment beyond last dose of study medication + 28 days will be excluded from efficacy summary. Lipid, hepatic fat fraction, and HbA1c assessments will be summarized by analysis visit according to the visit window defined in Appendix B. Other assessments will be summarized by nominal visit as collected in CRF.

Lipid (triglyceride and non-triglyceride), hepatic fat fraction, and HbA1c data will be mapped to analysis visit as specified in Appendix B. Assessments collected during randomized treatment period, will have analysis visit assigned according to the days relative to first dose date of randomized treatment period. Assessments collected during OLE period will have analysis visit assigned according to the days relative to first dose date of OLE period. The intent of these analysis visit windows is not to align with those prescribed for visit scheduling in the clinical study protocol but, rather, based on the protocol-defined target study day, to delineate mutually exclusive windows so that all efficacy assessments proximal to a particular study week can be integrated to best represent the patient's status during that period of the study. If a patient discontinued early from the treatment period but attended applicable landmark visits at Weeks 12, 13, 25, and etc. to collect lipid assessments, then those assessments collected at ET visit and during post-treatment follow-up period should be mapped to analysis visits as well, excluding assessment beyond 28 days after last dose of study medication. For the hepatic fat fraction and HbA1c data, data collected within the analysis visit window defined in Appendix B will be used. If there are multiple assessments within a visit window, only scheduled visit will be used, and the average will be used if there are multiple scheduled assessments, or the worst will be used if categorical result is collected in multiple scheduled assessments. If the assessments are all unscheduled, the visit nearest the scheduled date will be used, unless 2 visits are equally near, in which case the average will be used, or the worst will be used if categorical result is collected.

For efficacy data, local lab data will not be used unless central lab assessments are not available at certain visit. When calculating the baseline and analysis endpoints, only if the data from central lab is missing, then the local lab data will be utilized.

Safety assessments will be summarized by the nominal visit as collected in CRF. Multiple results with the same nominal visit will be averaged.

For safety lab, unscheduled assessment (both central lab and local lab) will not be included in the by-visit summaries, except for platelet analysis. Unscheduled results from the central lab will be used in the determination of baseline, laboratory abnormality summaries, shift from Baseline to worst post-baseline, and platelets reduction analyses. Local lab will be used in the determination of laboratory

abnormality summaries, shift from Baseline to worst post-baseline, and platelets reduction analyses, but not in baseline determination. For platelet, when central lab is not available at baseline, local lab result will be used in baseline determination.

3.2.2 Patient Population Analyzed

The following analysis sets will be used for the analysis of data as described within each analysis set.

Full Analysis Set (FAS): All patients who are randomized and received at least 1 dose of Study Drug in the randomized treatment period, and who have a baseline fasting triglyceride assessment (see definition in Section 3.2.3 for fasting lipid measurements). The FAS represents the practically-feasible intent-to-treat population as delineated in ICH Guideline E9.

Patients for whom the blind is broken during the trial will not be excluded from the FAS population. Patients will be analyzed in the treatment group to which they were randomized. Efficacy endpoint collected in both Randomized Treatment Period and OLE Period will be analyzed in FAS by the treatment group to which they were randomized. Although all patients receive volanesorsen during OLE period, assessment during OLE period will be analyzed according to the treatment assigned at previous Randomized Treatment Period. For example, if patient is assigned to the Placebo treatment at the Randomized Treatment Period, this patient will be analyzed in Placebo treatment group for both Randomized Treatment Period and OLE period.

Safety Set 1 (SAF1): All patients who are randomized and receive at least 1 dose of Study Drug (volanesorsen or Placebo) in the Randomized Treatment Period.

Patients will be analyzed in the actual treatment group patients received during the Randomized Treatment Period. Patients randomized to receive placebo, but incorrectly treated with volanesorsen will be counted in the volanesorsen group for the whole study period.

Safety Set 2 (SAF2): All patients who enter the OLE Period and receive at least 1 dose of Study Drug (volanesorsen) in the OLE Period.

As patients all receive volanesorsen in OLE period. In SAF 2, patients will be analyzed by the actual treatment received in the Randomized Treatment Period.

PK Population: All patients who are randomized, receive at least 1 dose of volanesorsen, and have at least one evaluable PK data, in either Randomized Treatment Period or OLE Period.

Patients will be analyzed in the actual treatment group patients received. Patients randomized to receive placebo, but incorrectly treated with volanesorsen will be counted in the volanesorsen group for the whole study period.

All primary, secondary [redacted] efficacy endpoints will be assessed in the FAS. Safety measures at Randomized Treatment Period and Randomized Treatment Period Post-Treatment Follow-up will be analyzed in SAF1. Safety assessment at OLE Period and OLE Post-Treatment Period will be analyzed in SAF2. PK endpoints will be assessed in the PK Population as applicable. Anti-drug antibody endpoints will be assessed in the SAF1.

Analysis populations will be summarized with counts and percentages by treatment group to which they were randomized, and overall.

3.2.3 Baseline and Endpoint Definition

The baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last non-missing measurement prior to Day 1 pre-dose assessment. If 1 of the 2 measurements is missing, then the other measurement will be assigned as the baseline value. If both are missing, then the baseline will be set as missing and the patient will be excluded from the FAS. Note that if on Day 1, there are multiple pre-dose assessments, then the last assessment with non-missing value will be used as the Day 1 pre-dose assessment.

The baseline for other measurements is defined as the last non-missing assessment prior to the first dose of Study Drug with the exception that platelet baseline is defined as the average of all assessments prior to the first dose of Study Drug.

Randomized Treatment Period and Open-Label Extension Period refer to one baseline, which is based on the pre-dose assessment of Day 1 in Randomized Treatment Period.

Efficacy by visit summary will include following time point, when data available. Both visit week and month will be presented.

Randomized Treatment Period Month 3 analysis time point is at the end of Randomized Treatment Period Month 3. For fasting lipid measurements, value at Month 3 is defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting lipid measurements. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing

Randomized Treatment Period Month 6 analysis time point is at the end of Randomized Treatment Period Month 6. For fasting lipid assessments, value at Month 6 is defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then value will be set as missing. .

Randomized Treatment Period Month 12 analysis time point is at the end of Randomized Treatment Period Month 12. For fasting lipid assessments, value at Month 12 is defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing. .

OLE Month 3 analysis time point is at the end of OLE Month 3. For fasting lipid measurements, value at OLE Month 3 is defined as the average of OLE Week 12 (OLE Day 78) and OLE Week 13 (OLE Day 85) fasting lipid measurements. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing. .

OLE Month 6 analysis time point is at the end of OLE Month 6. For fasting lipid assessments, value at OLE Month 6 is defined as the average of OLE Week 25 (OLE Day 169) and OLE Week 26 (OLE Day 176) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then value will be set as missing. .

OLE Month 12 analysis time point is at the end of OLE Month 12. For fasting lipid assessments, value at OLE Month 12 is defined as the average of OLE Week 50 (OLE Day 344) and OLE Week 52 (OLE Day 358) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing. .

OLE Month 15 analysis time point is at the end of OLE Month 15. For fasting lipid assessments, value at OLE Month 15 is defined as the average of OLE Week 64 (OLE Day 442) and OLE Week 65 (OLE Day 449) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing. .

OLE Month 18 analysis time point is at the end of OLE Month 18. For fasting lipid assessments, value at OLE Month 18 is defined as the average of OLE Week 77 (OLE Day 533) and OLE Week 78 (OLE Day 540) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing. .

OLE Month 24 analysis time point is at the end of OLE Month 24. For fasting lipid assessments, value at OLE Month 24 is defined as the average of OLE Week 102 (OLE Day 708) and OLE Week 104 (OLE Day 722) fasting assessments. If one visit is missing, then the other visit will be used. If both visits are missing, then the value will be set as missing. .

3.2.4 Patient Disposition and Demographics

Demographic, baseline characteristics will be summarized in FAS. Demographic including age, gender, ethnicity, race, region, Familial Partial Lipodystrophy (FPL) Group as entered on the Randomization CRF will be summarized using descriptive statistics. In addition, FPL Group derived based on the data entered on the Disease History CRF and the genetic testing results as below will be summarized.

- Patients with a pathogenic mutation in known FPL genes according to the University of Chicago data (for patients who consented to genetic testing) or historical genetic testing results (for patients who did not consent) will be assigned to Group 1.
- Patients who do not belong in Group 1 and have a family history of FPL or a similar fat distribution and/or history of fat loss in a first degree relative, plus at least 1 minor criterion as entered in the Disease History CRF will be assigned to Group 2. Minor criteria refers to protocol section 5.1 inclusion criteria.
- Patients who do not belong in Group 1 or Group 2 and have at least 2 minor criteria as entered in the Disease History CRF and a Screening BMI < 35 kg/m^2 will be assigned to Group 3.
- Patients who do not fall into one of the categories above will be assigned to None.

Baseline characteristics includes: body weight, height at screening, BMI, fasting lipids results including [redacted] Baseline data will be listed for all randomized patients.

All screened patients will be included in the summary of patient disposition. The number of patients screened, randomized, dosed, number of patients included in each analysis set, completed treatment, discontinued treatment along with reasons for discontinuing treatment, entered post-treatment follow-up, completed post-treatment follow-up, and discontinued post-treatment follow-up along with reasons for early terminating post-treatment follow-up, will be presented for both randomized treatment period and OLE period by treatment group to which they were randomized, and overall.

Listing of patient disposition will also be provided for all randomized patients.

Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 19.1 and will be summarized by system organ class and preferred term by treatment and overall for the SAF1 . Medical history will also be provided in the data listings.

3.3 Primary Analyses

Fasting triglyceride and change from baseline (absolute value and percentage of change) will be summarized by analysis visit using descriptive statistics in FAS. Descriptive summary statistics refers to section 3.2.1. Analysis visit includes baseline, endpoint as defined in section 3.2.3, and analysis week as specified in Appendix B.

3.3.1 Primary Endpoint Definition

The primary endpoint is the percent change in fasting triglyceride from Baseline to the primary analysis time point. The primary analysis time point is at the end of Month 3 where the value is defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments.

3.3.2 Analysis of Primary Endpoint

The primary efficacy analysis will be the comparison of the percent change from Baseline to Randomized Treatment Period Month 3 in fasting triglyceride between volanesorsen group and placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the randomization stratification factor (diagnosis of disease with or without genetics and family history) derived based on the Disease History CRF and genetic testing results and treatment group as factors and baseline fasting triglyceride as a covariate. In the ANCOVA model, triglyceride will be log-transformed. Patients with a missing primary endpoint will be excluded from primary efficacy analysis.

The primary efficacy analysis model (ANCOVA) will be repeated for the percent change from baseline in fasting triglyceride at Randomized Treatment Period endpoint month 6 and month 12.

A subgroup analysis of the primary efficacy analysis model (ANCOVA) will also be conducted in the group of genetically confirmed patients according to the University of Chicago data for patients who consented to genetic testing or historical data for patients who did not consent, and for patients with no mutation at month 3, month 6 and month 12. An interaction term of treatment group by derived FPL group will be included as a factor in the ANCOVA model.

The sample SAS code for the ANCOVA model can be found below:

```
**********************************************************************
* Note: Base = Baseline fasting triglyceride                         *
*       LOGBASE = Log-transformed baseline fasting triglyceride      *
*       PCHG = Percent change from Baseline at Month 3               *
*       TRTP = Treatment group: Placebo, volanesorsen                *
*       FPLGRPD = Derived FPL groups: 1 = FPL1, 2 = FPL2, 3=FPL3     *
*         FPL1 - Phenotype + Genetic Variants                        *
*         FPL2 - Phenotype + No Genetic Variant + Family Hist or Abnormal and  *
```

```
*                Similar Fat  + 1 Minor Criterion                          *
*      FPL3 - Phenotype + No Genetic Variant + No Family Hist or Abnormal and  *
*  Similar Fat + 2 Minor Criteria + BMI<35kg/m2                             *
*                                                                           *
*****************************************************************************
ods output lsmeans=lsm diffs=diff;
proc mixed data = M3TG;
   class TRTP (ref='Placebo') FPLGRPD;
   model PCHG = TRTP FPLGRPD LOGBASE /solution cl residual outp=predresid;
   lsmeans TRTP/e diff cl;
run;
```

3.3.3 Sample Size Consideration

Based upon prior clinical trial experience with volanesorsen, it is estimated that the standard deviation of the percent change in total fasting triglyceride is approximately 40%. With 20 volanesorsen patients and 20 placebo patients there would be approximately 80% power to detect a 40% difference in fasting triglyceride levels between treatment groups at an alpha level of 0.05, assuming 50% reduction in the volanesorsen treatment patients and 10% reduction in the placebo patients.

A sample size of 35 patients (20 active and 15 control) provides 92% power to detect a liver fat treatment difference of 4.7% based on a between patient standard deviation of 4% and a two-sided alpha of 0.05.

3.3.4 Planned Interim Analysis

There is no interim analysis planned for the study.

3.3.5 Incomplete or Missing Data

Patients with a missing primary endpoint will be excluded from primary efficacy analysis.

3.4 Secondary Analyses

Secondary efficacy endpoints will be summarized by visit using descriptive statistics in FAS. Descriptive summary statistics refers to section 3.2.1. Visit includes baseline, and nominal visit as collected in CRF, or according to the visit window defined in Appendix B for MRI, HbA1c, and lipid endpoints

3.4.1 Secondary Endpoint Definitions

The secondary endpoints include:

1. Percent Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI])
2. Change from Baseline in hemoglobin A1c (HbA1c)
3. A composite endpoint at Month 6 for percent of patients who achieve
   a. ≥ 40% reduction in fasting triglyceride, and
   b. ≥ 30% reduction of hepatic fat fraction percent
4. Change in patient-reported outcomes (PRO):
   - Patient-reported pain
   - Patient-reported hunger
   - QOL (EQ-5D, SF-36)

3.4.2 Analysis of Secondary Endpoints

3.4.2.1 Secondary Endpoint 1: Percent Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI])

Hepatic fat fraction (%), change from baseline, and percent change from baseline will be summarized by analysis visit using descriptive statistics in FAS. They will also be summarized separately by genetic mutation category: LMNA+PPARG, or neither. Descriptive summary statistics refers to section 3.2.1. Visit includes baseline and analysis visits according to the visit window defined in Appendix B.

The percent change in Hepatic Fat Fraction (%) from Baseline to month 6 and month 12 at Randomized Treatment Period will be analyzed using the similar ANCOVA model as for the primary efficacy analysis model (ANCOVA) .

A subgroup analysis of the ANCOVA will also be run for percent change in hepatic fat fraction in the group of genetically confirmed patients according to the University of Chicago data for patients who consented to genetic testing or historical data for patients who did not consent, and in patients with no mutation at month 6 and month 12 respectively.

3.4.2.2 Secondary Endpoint 2: Change from Baseline in HbA1c

HbA1c (%), change from baseline, and percent change from baseline will be summarized by analysis visit using descriptive statistics in FAS. They will also be summarized separately by genetic mutation category: LMNA, PPARG, or neither. Descriptive summary statistics refers to section 3.2.1. Visit includes baseline and analysis visits according to the visit window defined in Appendix B.

The change in HbA1c from Baseline to Randomized Treatment Period month 3, month 6, month 9 and month 12 will be analyzed using this similar ANCOVA model as for the primary efficacy analysis

A subgroup analysis of the ANCOVA will also be run for change in HbA1c from baseline in the group of genetically confirmed patients according to the University of Chicago data for patients who consented to genetic testing or historical data for patients who did not consent, and in patients with no mutation at month 3, month 6, month 9 and month 12 respectively.

3.4.2.3 Secondary Endpoint 3: Proportion of patients who achieve a >=40% reduction in fasting triglyceride from Baseline and >=30% reduction of hepatic fat fraction percent from baseline at Month 6

Frequency and proportion of patients who achieve a >=40% reduction in fasting triglyceride from baseline and >=30% reduction of hepatic fat fraction from baseline at Month 6 will be displayed.

3.4.2.4 Secondary Endpoint 4: Patient reported pain and hunger

No aggregated summary will be created.

3.4.2.5 Secondary Endpoint 4: Change from baseline in QOL (EQ-5D, SF-36)

No aggregated summary will be created.

[redacted]

3.6 Pharmacokinetic and Anti-drug Antibody Analysis

3.6.1 Pharmacokinetic Analysis

During the treatment period, blood samples for the determination of plasma volanesorsen concentrations will be collected from all patients prior to dosing, and at various times throughout the dosing and post-treatment follow-up period.

The sampling schedule is noted in the Plasma PK Sampling Schedule table below.

Plasma PK Sampling Schedule

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 19**	**Wk 26**	**Wk 32**	**Wk 38**	**Wk 44**	**Wk 52**
Study Day	1	22	50	85	127	176	218	260	302	358
Visit Window +/- Days	0	2	2	2	2	2	2	2	2	2
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-Dose	Pre-Dose

Patients continuing to first year of OLE period

Week	Wk 56	Wk 60	Wk 65	Wk 71	Wk 78	Wk 84	Wk 90	Wk 96	Wk 104	Wk 110	Wk 117
Study Day	386	414	449	491	540	582	624	666	722	764	813
Visit Window +/- Days	2	2	2	2	2	2	2	2	2	7	7
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-Dose	Anyti me	Anyti me

Patients continuing to second year of OLE period

Week	Wk 108	Wk 112	Wk 117	Wk 123	Wk 130	Wk 136	Wk 142	Wk 148	Wk 156	Wk 162	Wk 169
Study Day	750	778	813	855	904	946	988	1030	1086	1128	1177
Visit Window +/- Days	2	2	2	2	2	2	2	2	2	7	7
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anyti me	Anyti me

Plasma concentrations of volanesorsen, along with the scheduled (nominal) and actual sampling times (i.e., time from SC dosing) will be listed (when applicable) for each patient, by treatment, patient ID, patient anti-drug antibody (ADA) status, and IM onset (if applicable) as defined in Section 3.6.2, and day. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "0.00".

For all patients who receive volanesorsen treatment, trough (pre-dose) and post-treatment volanesorsen plasma concentrations will be summarized by study day, with and without stratification by IM status (positive/negative or unknown), using descriptive statistics (n, mean, SD, SEM, %CV, geometric mean, geometric %CV, median, minimum, and maximum). For the purpose of calculating typical descriptive statistics for plasma concentrations, all below the lower limit of quantification (BLQ) values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as "NA" (not applicable). At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

Mean (±SD) plasma volanesorsen concentration-time plots with stratification by anti-drug antibody status will be generated on semi logarithmic scales.

3.6.2 Anti-drug Antibody

Samples collected for anti-drug antibody (ADA) assessment at selected time points will be analyzed for anti-volanesorsen antibodies (i.e., anti-drug antibodies; ADA). Samples will be designated 'ADA positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise be deemed 'ADA negative'. Patients will be given 'positive' subject ADA status if they have at least one confirmed positive sample at any time before or during the treatment or post-treatment evaluation periods. Patients will be given 'negative' subject ADA status if all evaluated ADA sample results during the treatment and post-treatment evaluation periods are negative and they have at least one evaluable ADA result post-dose. Otherwise, patients will be given 'unknown' subject ADA status.

Sample ADA status (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen or placebo) will be listed by treatment.

Patient ADA status (positive/negative or unknown) for all evaluable patients, along with the study day associated with the first positive ADA status emerged (T_{first}, i.e., onset of ADA development), the last positive ADA status observed (T_{last}), the time of last evaluable ADA sample collected ($T_{last\ sampling}$), and max titer, will be listed by treatment.

Additionally, the ADA incidence (number) and incidence rate (percent) at each evaluated time point will be summarized by treatment, as the total number and percent of evaluated patients with antibody negative, positive, and unknown status. Similarly, the ADA incidence and incidence rate at patient level will be summarized by treatment. Furthermore, onset, and max titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), range by treatment for patients with positive ADA status.

Potential relationships between anti-drug antibody results (e.g., ADA status) and AE incidence will be evaluated in an exploratory manner.

3.7 Safety Analyses

Safety measures include: treatment exposure, adverse events, clinical safety lab, vital signs, physical examination, 12-Lead ECG, ECHO, concomitant medication use, and MRIs. Safety measures at Randomized Treatment Period and Randomized Treatment Period Post-Treatment Follow-up will be summarized in SAF1. Safety measures at OLE Period and OLE Post-Treatment Period will be summarized in SAF2.

Adverse events, lab shift table, and concomitant medication will be summarized by three analysis periods, including the Randomized Treatment Period using SAF1, Randomized Treatment Period Post-Treatment Follow-up among patients who do not continue to OLE using SAF1, and the combined OLE and OLE Period Post-Treatment Follow-up using SAF2. Start and end date of each analysis period is specified in the table below.

The rest safety measures will be summarized by nominal visit as collected in CRF, including vital sign, physical examination, clinical lab, Echocardiograph, ECG, and MRIs, etc.

Safety analysis period

	Period Start Date (inclusive)	Period End Date (inclusive)
Randomized Treatment Period (SAF1)	First dose date in Randomized Treatment Period	Volanesorsen group: Last dose date in the Randomized Treatment Period + one dose interval (7 days for weekly dosing schedule/ 14 days for bi-weekly dosing schedule) or first dose date in the OLE period -1 day, whichever is earlier. Placebo group: if patient continue to OLE, end date will be first dose date of volanesorsen in the OLE period - 1 day. Otherwise, last dose date in the Randomized Treatment Period + one dose interval (7 days for weekly dosing schedule/ 14 days for bi-weekly dosing schedule)
Randomized Treatment Period Post-Treatment Follow-up (SAF1, patients who do not continue to OLE)	Last dose date in the Randomized Treatment Period + one dose interval (7 days for weekly dosing schedule/ 14 days for bi-weekly dosing schedule) + 1 day	End date of Post-Treatment Follow-up Period
Combined OLE and OLE Period Post-Treatment Follow-up (SAF2)	Volanesorsen group: Last dose date in the Randomized Treatment Period + one dosing interval (7 day for weekly dosing schedule/ 14 day for bi-weekly dosing schedule) + 1 day or first dose date in the OLE period, whichever is earlier Placebo group: First dose date of volanesorsen in the OLE period	End date of Post-Treatment Period

If an AE starts in the Randomized Treatment Period and get worse in the combined OLE and OLE Period Post-Treatment Follow-up, the AE will be included in the summary of both period. If an AE starts in the Randomized Treatment Period and continues to the combined OLE and OLE Period Post-Treatment Follow-up in same or reduced severity, the AE will be included in the summary of first period only. If a concomitant medication starts in the Randomized Treatment Period and continues to

the combined OLE and OLE Period Post-Treatment Follow-up, the medication will be included in the summary of both periods

3.7.1 Imputation of Missing/Partial Dates

3.7.1.1 Adverse Events

For AEs, the following imputation rules will be applied to impute start dates under conservative principles:

- If year, month and day are all missing then assign the date of first dose of Study Drug
- If month and day are missing and year is:
    - the same as the year of the first dose of Study Drug then assign the month-day of first Study Drug
    - earlier than the year of the first dose of Study Drug then assign December 31
    - after the year of the first dose of Study Drug then assign January 1
- If only day is missing and month-year is:
    - the same as the month-year of the first dose of Study Drug then assign the day of first Study Drug
    - earlier than the month-year of the first dose of Study Drug then assign the last day of the month
    - after the month-year of the first dose of Study Drug then assign the first day of the month

Imputation will be performed only for the end date only if the day or month is missing (i.e., year is present) for a resolved AE as follows:

- If month and day are missing and year is
    - the same as the year of the last dose of Study Drug then assign the month-day of the last dose of Study Drug
    - otherwise, assign December 31
- If only day is missing then assign the last day of the month

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

Analysis period will be assigned by comparing the imputed AE start date with the period start/end date.

3.7.1.2 Prior/Concomitant Medications

For prior/concomitant medications, the following imputation rules will be applied to impute start dates under conservative principles:

- If year, month and day are all missing then assign the date of first dose of Study Drug

- If month and day are missing and year is:
  - earlier than the year of the first dose of Study Drug then assign December 31
  - otherwise, assign January 1
- If only day is missing and month-year is:
  - earlier than the month-year of the first dose of Study Drug then assign the first day of the month
  - otherwise, assign the last day of the month

Imputation will be performed only for the end date only if the day or month is missing (i.e., year is present) for a stopped prior/concomitant medication as follows:

- If month and day are missing then assign December 31
- If only day is missing then assign the last day of the month

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

Analysis period will be assigned by comparing the imputed medication start/end date with the period start/end date.

3.7.2 Adverse Events

All adverse events will be coded by the MedDRA dictionary version 19.1. Missing or partial dates will be imputed as outlined in Section 3.7.1. A treatment-emergent adverse event (TEAE) is defined as any event starting or getting worse on or after the first dose of Study Drug.

TEAE will be identified as follows based on the (imputed) AE start dates:

Case 1: If there is no "Formlink" link, and the AE (start date/time) occurs on or after the patient's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the patient's first dosing date/time, then the AE is not treatment-emergent.

Case 2: If there is a "Formlink" link between 2 AE records, then the 2 AE records will be chronologically ordered by AE start date/time and will be referred to as the "first" and the "second" AE respectively. AE severity (mild/moderate/severe) will then be compared pairwise.

Case 2a: The first AE record in the pair occurs before first dosing, and the second record occurs on/after dosing.

If the AE severity on the second record is worse than the severity on the first record or the severity on the second record becomes Serious AE, then only count the second AE as treatment-emergent. But, if the severity doesn't worsen (i.e., the second record severity is the same or less severe than the first record severity) or doesn't become SAE, then neither record is counted as treatment-emergent.

Case 2b: Both AE records in the pair occur on/after first dosing.

If the AE severity on the second record is worse than the severity on the first record or the severity on the second record becomes SAE, then count both records as treatment-emergent. But, if the severity doesn't worsen or doesn't become SAE, then only count the first record as treatment-emergent.

Case 2c: Both AE records in the pair occur before first dosing.

Neither AE is counted as treatment-emergent.

When counting the total number of treatment-emergent events, events linked together through change in severity will still be counted as separate events.

For AEs occurred during the Randomized Treatment Period, and the Combined OLE and OLE Post-Treatment Period , the frequency of patients with any incidence of AEs and the number of events will be summarized by analysis period, MedDRA preferred term and system organ class for:

- Any TEAE
- TEAEs potentially related to Study Drug. Related is defined as "Related", "Possible", or missing relationship to Study Drug
- Any treatment-emergent adverse event by severity. At each level of patient summarization, a patient with multiple events is counted only once according to the worst reported severity. Adverse events with missing severity will be categorized as "Missing" for this summary.
- TEAEs potentially related to Study Drug by severity
- Serious TEAEs
- Serious TEAEs potentially related to Study Drug
- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death.

Adverse event summaries will be presented by descending frequency of the percentage of patients in the Total column. An overview of AEs will be provided for all TEAEs. Treatment-emergent AEs, treatment-emergent SAEs, TEAEs that lead to treatment discontinuation, and TEAEs leading to death will be listed. Note that imputed dates will be used for defining TEAEs and classification of TEAEs into analysis periods. Originally reported dates will be used for listings.

For AEs occurred during Randomized Treatment Post-Treatment Period, the frequency of patients and number of events of any TEAEs, Serious TEAE will be summarized by MedDRA preferred term and system organ class.

In addition, an overview of adjudicated AEs will be provided for pancreatitis and MACE separately. Adjudicated events will also be listed.

3.7.2.1 Injection site reaction (ISR)

Injection site reaction (ISR) at injection site will also be summarized by treatment group and overall using the MedDRA coding system, by analysis period, system organ class and preferred term. Number and percent of patients reporting at least one ISR will be summarized also.

ISR is defined as any AE with MedDRA preferred term or verbatim that contains "INJECTION SITE", that starts on the day of injection and persist for at least 2 days, or start any time and persist for at least 2 days, AE resolution date – AE start date + 1 day should be great than two days. AE with preferred term or verbatim that contains "INJECTION SITE" and missing resolution date will also be included.

Percentage of injections leading to Injection Site Reaction will be summarized by treatment group and overall using descriptive statistics.

Percentage of injections leading to Injection Site Reaction will be calculated as follows for each patient: (A/B)*100, where A = number of injections leading to Injection site reaction (ISR), and B = total number of injections.

3.7.2.2 Flu-Like Reactions

Flu-like reactions (FLRs) will also be summarized by analysis period, treatment group and overall using the MedDRA coding system, by system organ class and preferred term. Number and percent of patients reporting at least one FLR will be summarized also.

Flu-like reactions are defined as AEs with following preferred term or verbatim: flu-like illness, chills, myalgia, arthralgia, pyrexia, feeling hot, or body temperature increased, starting on the day of injection or the next day.

Percentage of injections leading to flu-like reactions will be summarized by analysis period, treatment group, and overall using descriptive statistics.

Percentage of the injections leading to flu-like reactions will be calculated as follows for each patient: (A/B)*100, where A = number of injections leading to flu-like reactions, and B = total number of injections.

3.7.2.3 Adverse Events of Special Interest:

Treatment-emergent Bleeding, Hypersensitivity/Immunogenicity, Hepatotoxicity, Nephro-toxicity adverse events will be summarized using MedDRA preferred term and system organ class. Relationship between Treatment-emergent Bleeding event and presence of Concomitant Anti-Coagulant or Anti-Platelet Medication will be explored. Concomitant anti-coagulant or anti-platelet medications include medications that were taken before or on bleeding event onset date/time and stopped on or after bleeding onset date/time or ongoing at the end of study.

The Bleeding TEAE will be defined based on the Haemorrhages (SMQ) Export from MedDRA.

The Hypersensitivity/Immunogenicity TEAE is defined as AEs with either of two condition 1) meet Hypersensitivity (SMQ) Export from MedDRA, or 2) preferred term "Drug specific antibody" or "Drug specific antibody present" within system organ class "Investigations".

The Hepatotoxicity TEAE will be defined based on the Drug-related hepatic disorders – comprehensive search (SMQ) Export from MedDRA, excluding neoplasms.

The Nephrotoxicity TEAE will be defined based on, either the Acute Renal Failure (SMQ) Export from MedDRA, or Proteinuria (SMQ) Export from MedDRA.

Treatment-emergent bleeding adverse events will be listed as well.

3.7.3 Vital Signs Measurements

Vital signs will include weight, BMI, body temperature, heart rate, respiratory rate, and systolic, diastolic blood pressure, and [redacted]. Summary tables will be created by treatment group and overall to present the descriptive statistics (n, mean, standard error, standard deviation, median, P25, P75, minimum, and maximum) for vital sign values as well as the change from Baseline at each nominal study visit.

3.7.4 Laboratory Measurements

The following is the list of lab analytes that will be collected throughout the study:

- Chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, BUN (blood urea nitrogen), creatinine, creatinine clearance, estimated glomerular filtration rate, uric acid, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase,
- Hematology: red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, Platelets, white blood cells (WBCs), and WBC differential in both percentage and absolute count (Neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
- Coagulation: aPTT, PT, international normalized ratio (INR)
- Complement: C5a, Bb
- Other assessments: Troponin I, hsCRP, Sedimentation Rate, [redacted]
- Screening Tests: Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, FSH (women), serum βhCG (women), and HbA1c, TSH, T3, T4. The screening test data will only be displayed in patient listings.
- Urinalysis: color, appearance, specific gravity, pH, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocytes esterase, nitrate, and microscopic examination. For expanded urinalysis at certain visits, additional measurements will be performed including: total protein (quantitative), microalbumin, and β2-microglobulin. The expanded urinalysis data will be only displayed in patient listings.

Missing WBC differential absolute counts and percentages will be derived:

> If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophil counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Quantitative laboratory measurements reported as '< X', i.e. below the lower limit of quantification (BLQ), or '> X', i.e. above the upper limit of quantification (ULQ), or 'Cannot calc', i.e. outside the limit of quantification, will be converted to X (or limit of quantification) for the purpose of quantitative summaries.

The MDRD equation will be used to calculate estimated Glomerular Filtration Rate (GFR) base on central lab serum creatinine (µmol/l) as:

eGFR (mL/min/1.73m^2) = 32788 × Serum Creatinine (µmol/l) ^ (-1.154) × Age ^ (-0.203) × (1.210 if Black or African American) × (0.742 if female).

Chemistry, hematology, coagulation, complement, other assessments and quantitative urinalysis (result, change from Baseline) will be summarized using descriptive statistics (n, mean, standard error, standard deviation, median, P25, P75, minimum, and maximum) and urinalysis dipstick protein will be summarized by frequency counts by treatment group, overall, and by nominal study visit.

The number and percent of patients falling in each of the following category after first dose will be tabulated by treatment group and overall, for each analysis period:

- The higher of ALT > 3 x upper limit of normality (ULN) or ALT > 2 x Baseline
- ALT/AST > 3 x ULN
- ALT/AST > 5 x ULN
- ALT/AST > 8 x ULN
- ALT/AST > 10 x ULN
- ALT/AST > 20 x ULN
- ALT > 3 x ULN - ≤ 5 x ULN
- ALT > 5 x ULN - ≤ 10 x ULN
- ALT > 10 x ULN - ≤ 20 x ULN
- Total bilirubin > 2 x ULN
- ALP > 2 x ULN and (baseline ALP < 2 x ULN or baseline ALP missing)

The number and percent of patients falling in each of the following categories based on confirmed results after first dose will be tabulated by treatment group, and overall for each analysis period (a confirmed value is based on a consecutive lab value performed on a different day to, but within 7 days of, the initial value. If that value is in the same or worse category then the initial value is confirmed. If the consecutive value is in a better category then the initial value is confirmed using the consecutive value category. If there is no retest within 7 days then the initial value is presumed confirmed. If there are multiple results on the same day, then the worst value will be utilized in the analysis):

- The higher of ALT/AST > 3 x ULN or ALT/AST > 2 x Baseline, which is confirmed
- ALT/AST > 3 x ULN, which is confirmed
- ALT/AST > 5 x ULN, which is confirmed
- ALT/AST > 10 x ULN, which is confirmed
- ALT/AST > 20 x ULN, which is confirmed

For patients having confirmed 3-fold or greater elevations above the ULN for ALT or AST, a listing of all of the ALT, AST, total bilirubin, INR, and alkaline phosphatase records will be provided. Other liver abnormalities including elevation of ALT (> 3 x ULN) accompanied by elevated total bilirubin (> 2 x ULN), elevation of ALT (> 3 x ULN) accompanied by INR > 1.5 x ULN, elevation of ALT (> 3 x ULN) accompanied by elevated total bilirubin > 2 x ULN and ALP < 2 x ULN, and elevation of ALT/AST in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue will be reviewed by the study team and summarized if needed.

The following hematology and hepatic enzymes lab results will be graded based on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007), and the incidence of shift from Baseline to worst post-baseline value will be summarized for each analysis period. Post-baseline lab results are defined as any assessment taken after the first dose. If a patient is missing a baseline value but has a post-baseline value, then the baseline assessment will be labeled as "unknown". Likewise, if a patient has a baseline value but has no post-baseline values, then the worst value will be labeled as "unknown". Number and proportion of patients with shift from baseline to worst post-baseline values based on the confirmed results by toxicity grade for GFR, ALT, AST, and platelets will also be tabulated.

- Hemoglobin: shift from Baseline to minimum post-baseline value
- WBCs: shift from Baseline to minimum post-baseline value
- Platelets: shift from Baseline to minimum post-baseline value
- Creatinine: shift from Baseline to maximum post-baseline value
- BUN: shift from Baseline to maximum post-baseline value
- eGFR: shift from Baseline to minimum post-baseline value
- Proteinuria: shift from Baseline to worst post-baseline value
- ALT: shift from Baseline to maximum post-baseline value
- AST: shift from Baseline to maximum post-baseline value
- Alkaline phosphatase: shift from Baseline to maximum post-baseline value
- Total bilirubin: shift from Baseline to maximum post-baseline value

eGFR will be graded using the following criteria:

- $\geqslant$ 90 mL/min/1.73m^2
- $\geqslant$ 60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2
- $\geqslant$ 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2
- $\geqslant$ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2
- < 15 mL/min/1.73m^2

The incidence of platelet reduction from Baseline $\geq$ 30% and $\geq$ 50% and each of the following categories will be summarized for the worst post-baseline value for patients in SAF 1 and SAF2, by analysis period: any 2 occurrences of platelet count < 140,000/mm^3, any single occurrence of platelet count < 100,000/mm3, , 100,000/mm^3 to < 140,000/mm^3, 75,000 to < 100,000/mm^3, 50,000 to < 75,000/mm^3, 25,000 to < 50,000/mm^3, 0 to < 25,000/mm^3. These categories will be summarized based confirmed values as well.

A listing will be provided for patients who terminated treatment due to a protocol-defined stopping rule (see Protocol Section 8.6 for details) with categories (liver chemistry elevation, renal function test results, platelet count results) and narratives.

3.7.5 Exposure

Treatment duration and amount of Study Drug received will be summarized by Randomized Treatment Period and OLE period, and by treatment group and overall for the SAF1 and SAF2. Treatment duration is defined as the last day on Study Drug in a specific period minus the first day on Study Drug in the analysis period plus one day.

Compliance to Study Drug will be summarized by descriptive statistics by treatment, and in total, for each period.

Compliance will be calculated as follows:

> 100 x (number of injections of Study Drug) / (number of injections scheduled during the treatment period).

Note that number of injections scheduled during the treatment period will be calculated as the Study Week of the last dose for patients did not get dose adjustment to biweekly. For patients who got dose adjustment to biweekly, if the dose adjustment started at Week x, then number of injections scheduled during the treatment period will be calculated as x plus the largest integer that is less than or equal to (study week of the last dose minus x) divided by 2, [number of weeks on weekly dose + integer of (number of weeks on bi-weekly dose)/2]

For early withdrawals/terminations, the number of injections will be calculated for the period up to their withdrawal/termination.

3.7.6 Physical Examination

Abnormal changes in physical examinations that are deemed clinically-significant by the Investigator will be classified as adverse events. Physical examination results will be listed by labeled visit.

3.7.7 12-Lead Electrocardiogram

ECGs will be performed in triplicate at the visits indicated in the protocol Schedule of Procedures. The ECG data will include ventricular rate, PR interval, QRS duration, QT and corrected QT intervals, and overall interpretation. For the continuous variables, the average of measurements at a given visit will be used for analysis. For overall interpretation, the worst categorical results of triplicate results and the associated findings will be used for analysis. For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, P25, P75, minimum, and maximum) of the results, as well as the change from Baseline to each study visit, will be presented by treatment group, and overall in summary tables; for the categorical responses to overall interpretation, counts and percentages will be provided.

All the data collected in triplicate will be listed.

3.7.8 Echocardiogram

Echocardiogram results will be listed.

3.7.9 Concomitant Medications

All medications will be coded by WHODrug (Version Mar2014). Medications start and stop dates that are recorded on the Prior and Concomitant Medications CRF will be used to determine whether the medications are prior or concomitant to the treatment period. Missing or partial dates will be imputed as outlined in Section 3.7.1. Prior medications include medications started prior to the first dose of Study Drug regardless whether continued while on treatment or not. Concomitant medications include medications that patients exposed to on or after the first dose of Study Drug. A prior medication with an imputed stop date that is missing or on or after date of first dose of Study Drug will also be considered as a concomitant medication. Medications will be classified based on (imputed) start and (imputed) stop dates as follows:

1) Prior Medication

Start Date	**End Date**
< FDD	Any non-missing stop date
	Missing

FDD = Date of First Dose of Study Drug

2) Concomitant Medication

Start Date	**End Date**
< FDD	≥ FDD
	Missing
≥ FDD	Any non-missing stop date
	Missing

FDD = Date of First Dose of Study Drug

Medication verbatim terms will be coded to Anatomical Therapeutic Chemical (ATC) classification and preferred name using the World Health Organization Drug Dictionary (Version Dec 2014).

Prior and concomitant medications will be summarized separately for each analysis period by ATC class, preferred name, treatment group and overall with counts and percentages, sorting by decreasing frequency in the overall column.

Additionally, antidiabetic medication changes during each analysis period, which include those medications that are started, stopped, or changed dose during the analysis period, will be summarized by ATC class, preferred name, analysis period, treatment group and overall with counts and percentages for the SAF1 and SAF2 , sorting by decreasing frequency in the overall column.

Prior and concomitant medications will be displayed in patient listings for all randomized patients. Note that imputed dates will be used for prior and concomitant medications classification. Originally reported dates will be used for listings.

3.7.10 MRIs

The hepatic volume and splenic volume as assessed by MRI will be summarized using descriptive statistics by analysis windows outlined in Appendix B. Liver (hepatic fat fraction, [redacted]) and spleen MRIs will also be displayed in patient listings for all randomized patients.

3.8 Changes in the Planned Analysis

Study treatment is discontinued before completing the protocol specified treatment period. The following protocol specified analysis will not be conducted at the final analysis.

1. Protocol section 10.3 "Per Protocol Set (PPS)", in final analysis, Per Protocol Set will not be classified. All analysis endpoint will not be assessed in PPS.

2. Protocol section 10.6.3 primary efficacy analysis, patient with missing primary endpoint will be excluded from primary efficacy analysis (ANCOVA). Protocol specified imputation method and sensitivity analysis to assess the robustness of the primary analysis results will not be conducted. For secondary efficacy analysis (patients who achieve a $\geq$ 40% reduction in fasting triglyceride from Baseline and $\geq$ 30% reduction of hepatic fat fraction percent from baseline at Month 6), protocol specified statistical comparison will not be conducted, only descriptive summary will be provided. The change from baseline in fasting triglycerides, hepatic fat fraction, and HbA1c will be assessed using ANCOVA model with derived FPL based off of genetic confirmation as a stratification factor. A subset analysis will look at the change from baseline in fasting triglycerides, hepatic fat fraction, and HbA1c by gene mutation of LMNA + PPARG and no mutation. The ANOCOVA model used for this analysis will include an interaction term between treatment and FPL group

3. Protocol section 10.1.2 states that Disease burden score is one of secondary efficacy endpoint. However this patient-reported outcome is not collected in the study. Disease burden score will not be summarized.

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5 APPENDICES

Appendix A – Data to be reviewed by DSMB

The data to be reviewd by DSMB is referenced to the CS17 DSMB Charter v1.0-Aug 6, 2015.

Data for Review[1]	Listings	Tables[2]	Figures
Demographics and Baseline Characteristics	X	Counts and summary statistics	
Disposition	Reasons for withdrawal from study	Counts overall (and by stratum as needed)	
Medical History	X		
Concomitant Medications	X		
Study Drug Exposure	Doses received and reasons for withdrawal from drug		
Protocol deviations	Deviations will be listed by type[3]		
Treatment Emergent AEs	X	By MedDRA system organ class, MedDRA term and severity	
Treatment Emergent Related AEs	X	By MedDRA system organ class, MedDRA term and severity	
SUSARs	Listing and narratives		
Deaths	Listing and narratives		
Patients that have reached a protocol-defined stopping rule	Listing and narratives		
Adjudicated MACE Events	Listing and narratives		
Adjudicated Acute Pancreatitis Events	Listing and narratives		
Vital Signs (SBP, DBP, HR)	X		
Lab values (clinical chemistry, coagulation, hematology, hsCRP, complement, troponin-I, HbA1c)	X		Key parameters will be graphed by value and visit for individual patients[4]
Urinalysis	X		Urine protein (dipstick) will be graphed by value and study day for individual patients
ECG parameters and findings	X		
Echocardiogram findings	X		

1. Additional data may be requested by DSMB and will be provided in agreed upon format
2. Summary tables will be produced as number of patients enrolled allow
3. Protocol Deviations will be listed by the following types:
    - Eligibility criteria not met
    - Study drug administration errors

- Patient not withdrawn according to protocol requirements
- Missed laboratory sample collection for safety and/or primary endpoint
- Safety end/or primary endpoint procedures that are missed or improperly conducted
- Disallowed/restricted concomitant medications
- Non-compliance to stopping rules
- Improper informed consent procedures

4. The following key parameters will be presented graphically:
    - Alanine aminotransferase (ALT)
    - Aspartate aminotransferase (AST)
    - Alkaline phosphatase (ALP)
    - BUN
    - Total, direct and indirect bilirubin
    - Creatinine
    - Hemoglobin
    - Lymphocyte, absolute
    - Neutrophil, absolute
    - Platelet count
    - White blood cell count

Appendix B – Efficacy measurement analysis visit window

Efficacy Measure	Study Period	Period week	Target Day	Study Day Window
Lipid	Screening		-56 to -15	≤ -15
	Qual Visit		-14 to -7	-14 to < 1
	Randomized Treatment Period	1	1	1
		4	22	2 to 36
		8	50	37 to 64
		12	78	65 to 82
		13	85	83 to 106
		19	127	107 to 148
		25	169	149 to 173
		26	176	174 to 197
		32	218	198 to 239
		38	260	240 to 281
		44	302	282 to 323
		50	344	324 to 351
		52	358	≥ 352
Lipid	Open Label Extension (OLE)	4	22	1 to 36
		8	50	37 to 64
		12	78	65 to 82
		13	85	83 to 106
		19	127	107 to 148
		25	169	149 to 173
		26	176	174 to 197
		32	218	198 to 239
		38	260	240 to 281
		44	302	282 to 323
		50	344	324 to 351
		52	358	352 to 372

Efficacy Measure	Study Period	Period week	Target Day	Study Day Window
		56	386	373 to 400
		60	414	401 to 428
		64	442	429 to 446
		65	449	447 to 470
		71	491	471 to 512
		77	533	513 to 537
		78	540	538 to 561
		84	582	562 to 603
		90	624	604 to 645
		96	666	646 to 687
		102	708	688 to 715
		104	722	≥ 716
	Post-Treatment Follow-up	7	43	1 to 64
		13	85	≥ 65

Efficacy Measure	Study Period	Period week	Target Day	Study Day Window
MRI liver (hepatic fat fraction)	Screening		-42 to 1	≤ 14
	Randomized Treatment Period	Month 6 (25, 26)	169-176	109 to 236
		Month 12 (50, 52)	344-358	284 to 418
	Extension Open Label	Month 6 (25, 26)	169-176	109 to 236
		Month 12 (50, 52)	344-358	284 to 418

Efficacy Measure	Study Period	Period week	Target Day	Study Day Window
[redacted], HbA1c	Screening		-56 to -15	≤ -15
	Randomized Treatment Period or Open Label Extension Period	1	1	1
		Month 3 (13)	85	55 to 115
		Month 6 (26)	176	146 to 206
		Month 9 (38)	260	230 to 290
		Month 12 (52)	358	328 to 388

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