Official Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-LRx) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

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Sponsor:

Akcea Therapeutics, Inc.

22 Boston Wharf Road, 9th Floor

Boston, MA 02210

Collaborator:

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

Statistical Analysis Plan

ISIS 703802–CS2

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

Date: December 12, 2019

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Akcea Therapeutics, Inc.

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

Compound Name: ISIS 703802 (AKCEA-ANGPTL3-L_{Rx})

Protocol: ISIS 703802–CS2

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

Protocol Issue Date: Amendment 3 – March 21, 2019

Signature: [redacted] Date: 12DEC2019

[redacted]
Akcea Therapeutics, Inc.

Signature: [redacted] Date: 12 Dec, 2019

[redacted] MD, PhD
[redacted]
Akcea Therapeutics, Inc.

Signature: [redacted] Date: 12 Dec 2019

[redacted] PhD
[redacted]
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]
Reviewer	[redacted] Project Role: [redacted]
Reviewer	[redacted] Project Role: [redacted]

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	2019DEC12	Final document

ABBREVIATIONS

AE	Adverse Event
ADA	Anti-drug Antibody
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ApoA-I	Apolipoprotein A-I
ApoB	Apolipoprotein B
ApoC-III	Apolipoprotein C-III
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
FFA	Free Fatty Acid
FLR	Flu-like Reaction
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GalNAc	*N*-acetyl galactosamine

GGT	Gamma-Glutamyl Transferase
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-apoC-III	High-Density Lipoprotein-Apolipoprotein C-III
HDL-C	High-Density Lipoprotein Cholesterol
HOMA-IR	Homeostasis Model Assessment-Estimated Insulin Resistance
ICH	International Council on Harmonisation
INR	International Normalized Ratio
ISR	Injection Site Reaction
IxRS	Interactive Voice/Web-Response System
LCRIS	Local Cutaneous Reactions at Injection Site
LDL-C	Low-Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein(a)
MAR	Missing at Random
PAT	Primary Analysis Time Point
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
QW	Once Weekly
Q4W	Once Every 4 Weeks
SAE	Serious Adverse Event
SAT	Subcutaneous adipose tissue
SI	International System of Units
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
TG	Triglyceride(s)
ULN	Upper Limit of Normal
VAT	Visceral Adipose Tissue
VLDL-C	Very Low-Density Lipoprotein Cholesterol
WHR	Waist-to-Hip-Ratio

1 INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the Akcea Therapeutics, Inc. study with Protocol Number ISIS 703802-CS2. The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Amendment 3 (March 21, 2019)
- electronic Case Report Form (eCRF), Version 10 (June 21, 2019)

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

Protocol ISIS 703802-CS2 is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, dose-ranging study being conducted in the United States and Canada. After screening, up to 96 eligible patients randomized to 1 of the 3 dosing cohorts. Each cohort has a 3:1 ratio to receive ISIS 703802 or matching volume of placebo by SC injection as below.

Cohort A (20 mg QW, n = 32): 20 mg ISIS 703802 or placebo (3:1) once every week for 26 doses.
Cohort B (40 mg Q4W, n = 32): 40 mg ISIS 703802 or placebo (3:1) once every 4 weeks for 6 doses.
Cohort C (80 mg Q4W, n = 32): 80 mg ISIS 703802 or placebo (3:1) once every 4 weeks for 6 doses.

Following End-of-Treatment (EoT) assessments, all patients will then enter a 13-week post-treatment follow-up period.

The primary safety and efficacy analysis time point is at Week 27 for patients who received weekly dosing and at Week 25 for patients who received every 4-week dosing.

1.2 Objectives

1.2.1 Primary Objective

To assess the effect of different doses and dosing regimens of ISIS 703802 on reduction in fasting triglycerides.

1.2.2 Secondary Objectives

To evaluate the safety and tolerability of ISIS 703802.

To evaluate the effect of ISIS 703802 on changes from Baseline to EoT for glucose and lipid metabolism, and liver fat.

To evaluate pharmacokinetics (PK) of ISIS 703802 across different doses and dose regimens.

To evaluate the effect of ISIS 703802 on changes from Baseline to selected timepoints for biomarkers related to liver inflammation, adipokines and body composition.

1.3 Hypotheses

The strategy of treating patients with hypertriglyceridemia, T2DM and NAFLD with ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) is to reduce the levels of ANGPTL3 protein secreted by the liver, a primary organ for GalNAc conjugated antisense oligonucleotide (ASO) distribution after systemic delivery. It is hypothesized that by decreasing the amount of liver-derived ANGPTL3 protein circulating in the plasma, by treatment with ISIS 703802, the following will be observed: lowered levels of triglyceride-rich lipoproteins and low density lipoprotein cholesterol (LDL-C), increased high density lipoprotein cholesterol (HDL-C), and improved glycemic control including ameliorated insulin resistance in T2DM patients. Thus, the expected outcomes include a decrease in liver fat content in NAFLD, improved glycemic control in T2DM, and reduction in triglyceride levels expected to reduce CV risk.

The primary endpoint (fasting triglyceride level) will be tested. The null hypothesis of no difference between each ISIS 703802 treatment dose and placebo, in the percent change in fasting triglyceride level from Baseline to the primary analysis time point (PAT), will be evaluated by an ANCOVA model analysis. The analysis of the primary efficacy endpoint will be conducted using two sided tests with an alpha of 0.05. The primary study hypothesis will be formally evaluated after all patients have completed the EoT assessments.

A final analysis will be conducted after all patients have completed their post-treatment follow-up visits.

1.4 Endpoints

The primary efficacy analysis time point is at Week 27 for patients who received weekly dosing and at Week 25 for patients who received every 4-week dosing.

1.4.1 Primary Endpoint

Percent change in fasting triglyceride level from baseline to the primary analysis time point.

1.4.2 Secondary Endpoints

Evaluate the effect of ISIS 703802 on changes from baseline to the primary analysis time point for:

- Change and percent change in ANGPTL3 protein, total cholesterol (TC), LDL-C, HDL-C, very low density lipoprotein cholesterol (VLDL-C), non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apoB (apoB-48, apoB-100)), apolipoprotein C-III (apoC-III), apolipoprotein A-1 (apoA-I), free fatty acids (FFA), lipoprotein(a) [Lp(a)]
- Change in fasting plasma glucose, fasting insulin, HOMA-IR, HbA1c, fructosamine and glycated albumin
- Change and percent change in weight, systolic and diastolic blood pressure (SBP and DBP)
- Change and percent change in hepatic fat fraction (HFF) by MRI-PDFF
- Proportion of patients reaching hepatic fat fraction (HFF) < 5% or ≤8% by MRI-PDFF

- Change in Fatty Liver Index (FLI)
- Change in ALT and AST
- Change in adipokines such as leptin, or adiponectin, and phospholipids (e.g. ceramides, sphingolipids, diacylglycerol)
- Change in body composition as measured by single slice MRI of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), waist circumference, WHR (waist-to-hip ratio) and BMI

[redacted]

1.4.4 Safety Endpoints

- AEs
- Vital signs
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Electrocardiogram (ECG)
- Use of concomitant medications
- Exposure and Compliance
- Pharmacokinetics (PK) and Immunogenicity (anti-drug antibody formation)

The details on the safety analyses are discussed in section 3.5.

2 PROCEDURES

2.1 General Overview of Procedures

The study for an individual patient will generally consist of the following periods:

- A Screening Period (up to 5 weeks), including a 4-week diet stabilization phase, where appropriate
- A Treatment Period (up to 26 weeks) during which Study Drug (ISIS 703802 or placebo) will be administered per assigned cohort by SC injection

- A Post-treatment Follow-up Period (13 weeks)

Physical exams, vital signs, ECG, blood and urine samples will be collected regularly throughout the study for safety, efficacy, and PK analysis. Appendix B in Protocol shows a list of analytes required for the study and Appendix C in Protocol details the PK sample schedules. Details on assessments information are in protocol section 6.2.

2.1.1 Screening Period

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. Patients will be advised to maintain diet and exercise routines and remain on a stable regimen of diabetes and lipid medications (if they are already taking any). As part of the Screening Period, patients not already on a stable diet will have 4 weeks of diet run-in, followed by a qualification visit during which final eligibility assessments will be performed. Patients on stable diet known to the investigator and followed at the site may go from Screening to qualification without a 4-week diet stabilization phase. At the qualification visit, triglycerides will be measured. MRI will be obtained during screening once all other eligibility criteria are met to assess liver fat content.

Patients meeting eligibility criteria at Screening and having qualifying triglycerides and MRI results, defined as having greater than 8% liver fat assessed by MRI-PDFF (via central reviewer) will return to the clinic on Day 1. Triglycerides and MRI results must be available prior to randomization and administration of the first dose of Study Drug. On confirmation of eligibility and prior to randomization, patients will also undergo a 24 hr urine collection for creatinine, albumin, and protein as a baseline assessment.

2.1.2 Treatment Period

Patients assigned to Cohort A will receive a single SC dose of ISIS 703802 or placebo every week for a total of 26 doses. Patients assigned to Cohorts B and C will receive a single SC dose of ISIS 703802 or placebo every 4 weeks for a total of 6 doses. Patients will return regularly for outpatient visits throughout the treatment period according to the Schedule of Procedures (in Protocol Appendix A).

2.1.3 Post-Treatment Follow-Up Period

Following the end of the treatment period, patients will then enter a 13-Week Post-Treatment Follow-up Period and will return to the Study Center for outpatient evaluations according to the Schedule of Procedures (in Protocol Appendix A).

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 patients may begin treatment prior to randomization and assignment of a unique patient identification number.

Using an Interactive Web-Response System (IWRS), eligible patients will be randomized in a 1:1:1 ratio to 1 of the 3 parallel dose cohorts (Cohorts A, B, or C). Within each dose cohort, patients will be randomized in a 3:1 ratio to receive ISIS 703802 or matching volume of placebo, respectively.

A permuted block schedule will be used. The randomization schedule will be generated and held by an independent 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 Harmonisation (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

In order to ensure maintenance of the study blind, following randomization the results of efficacy parameters consisting of lipid panel results including apoA-I, apoB (100, 48), apoC-III, TC, FFA, LDL-C, HDL-C, non-HDL-C, VLDL-C, triglycerides and Lp(a), PK and selected PD panel results, ANGPTL3 and MRIs will be blinded to the Akcea study team, Clinical Research Organization (CRO) study team, Investigators, Study Center personnel and patients until after database lock for EoT. After Sponsor's unblinding post completion of treatment period, blinded study personnel will continue to oversee the study until all patients completed the study.

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's 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 US and Canada health authorities. 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.

Details about the safety monitoring rules, stopping rules and dose adjustment for clinical safety parameters are in the protocol sections 8.5-8.7. Details about Adverse Events Monitoring are in the protocol sections 9.4.

2.4.2 Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected during this study. Based on its ongoing assessment of the safety and tolerability, 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.

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 Trennic Data Services as 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 check the validity of the data entered and prompt for missing data) are executed and automatic data queries are generated. The Sponsor will perform blinded review of data for accuracy and validity; also generating additional queries in the EDC system, where necessary. The queried data is corrected or an explanation concerning the query is provided in the EDC system. After all data are 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 are not stored in the EDC system but will be transferred to Trennic Data Services.

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

The Sponsor is responsible for the management and review of the PK and ADA data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK and ADA data are not stored in the EDC system but will be transferred to Akcea Therapeutics, Inc. or designee as external data.

2.5.4 Other Data

The Sponsor is responsible for the management of the MRI data and other external data. Data will also not be stored in the EDC system but will be transferred to Akcea Therapeutics, Inc. or designee as external data.

3 ANALYSIS PLAN

3.1 Statistical Design Summary

This is a multi-center, randomized, double blind, placebo-controlled study.

The study hypotheses will be formally evaluated at the planned EoT analysis. The primary and secondary endpoints for the study will be recorded at Week 27 for Cohort A (ISIS 703802 and

Placebo) and Week 25 for Cohorts B and C (ISIS 703802 and Placebo) and where applicable may be based on analysis windowing rules found in Appendix A.

The treatment groups proposed in this analysis are defined as ISIS 703802 20 mg weekly (20 mg QW), ISIS 703802 40 mg every 4 weeks (40 mg Q4W), ISIS 703802 80 mg every 4 weeks (80 mg Q4W) and Pooled Placebo, defined as the combined group of placebo patients from the 3 randomized cohort groups.

EoT analyses will be conducted on data obtained through the data cut-off date, defined as the date of the last EoT visit. The database will be queried and data cleaning performed on all data, with database lock of all data, at which point the treatment code is unblinded and the EoT analyses are performed.

A final analysis will be performed after all data from the 13-week post treatment follow-up period are collected.

3.2 General Overview of Analyses

This analysis plan describes the reporting of data at the end of the treatment and study (unless specified otherwise).

3.2.1 General Conventions

All reporting will be performed in SAS version 9.3 or higher.

All electronic case report form (eCRF) data and 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 enrolled into the study, and will be sorted by treatment group, patient ID, visit, and time point (where appropriate).

3.2.2 Reporting Conventions

Efficacy results will be summarized under the treatment to which patients were randomized. Safety and PK results will be summarized under the treatment which patients actually received. Should there be any cases after unblinding in which a patient received treatment other than what was randomized, such cases will be discussed in the study report and noted in footnotes where applicable.

All tables will present the population frequencies in each treatment group and/or subgroup (where appropriate) and will indicate the number of patients with non-missing data and the denominators for percentages.

Descriptive summary statistics including n, mean, median, standard error, standard deviation, interquartile range (25th percentile, 75th percentile), range (minimum, maximum), Mean 95% confidence interval (CI) for continuous variables, and counts and percentages for categorical variables, will be used to summarize data by treatment group. Summaries of pharmacokinetic concentrations and parameters will also present coefficient of variation (CV%), geometric mean and geometric CV%. 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.

Except summaries for PK parameters, precision for displays will use the following conventions. Means, percentiles (e.g., median, 25th percentile, 75th percentile), least squares means, difference in

least squares means will be displayed to one more decimal place than measured values. Standard deviations and standard errors will be displayed to two more decimal places than measured values. The minimum, maximum and confidence intervals will be displayed using the same number of decimal places as the recorded values. All raw values presented in listings will be displayed to the measured precision. Percentages will be displayed to one decimal place. For PK concentrations and parameters, mean, standard deviation, standard error, geometric mean, median, minimum, and maximum values will be presented to 3 significant digits and CV% and geometric CV% will be presented to one decimal place. p-values will be displayed to 4 decimal places. p-value <0.0001 presents as "<0.0001". p-value >0.9999 presents as ">0.9999". Confidence intervals (CIs) will be presented using a comma separator rather than a dash.

Age will be presented in years. Weight will be presented in kg. Height will be presented in cm. Temperature will be presented in °C. Laboratory listings will keep original unit. Descriptive summary tables by visit will be based on lab original units as recorded in the central laboratory dataset. Where potentially there is more than 1 original unit for a parameter in the central laboratory dataset, the parameter's unit will be converted to the unit the majority of the results are reported in. Table 1 and Table 2 specifies how data will be considered.

Table 1: Summary of Lab Data per Type of Output

	Type of Outputs	**Data source**	**Unit**	**Visits**
Listings	Listings of lab data	Central and local lab in separate listings	Original Unit	SCH + USCH visits
Tables, Figures	All efficacy endpoints (primary, secondary, [redacted])	Central lab	Original Unit	analysis SCH + USCH within visit window
	Descriptive summary of platelet count data	Central and local lab, separate tables and figures	Original Unit (/mm^3)	nominal SCH visits including repeated records at same visits (average all the records for each visit by central lab or by local lab)
	Descriptive summary safety lab data other than platelet counts	Central lab	Original Unit	nominal SCH visits
	Safety shift tables	Central and local lab	Per mock shells	nominal SCH + USCH visits
	Abnormalities lab tables	Central and local lab	Per mock shells	nominal SCH + USCH visits
	SCH: scheduled; USCH: unscheduled			

Table 2: Summary of Lab Data per Type of Value

Type of values	Data source	Unit	Visits
Baseline for platelet count	Central and local lab	Original Unit (/mm^3)	SCH + USCH visits prior to the first dose of Study Drug
Baseline for ALT and AST	Central lab	Original Unit	nominal SCH + USCH visits; the average of Day 1 pre-dose assessment and the last non-missing measurement prior to Day 1 pre-dose assessment
Baseline for other safety labs	Central lab	Original Unit	analysis/nominal based on SCH + USCH visits when selected as last non missing prior to first dose of Study Drug
Confirmed lab value	Central and local lab	per Mock Shell	nominal SCH + USCH visits
SCH: scheduled; USCH: unscheduled			

3.2.3 Analysis Visit Summarization

All primary and secondary efficacy endpoints except vital signs, leptin/adiponectin and ALT/AST will be mapped by analysis visit and record selection rules, as specified in Appendix A. For display and analyses purposes, the assessments will be displayed by the scheduled visits as described in the protocol and will use the analysis visit algorithm where necessary. Other safety assessments will be summarized by the nominal visit as collected in the data and will not use visit analysis window mapping.

Summary table over time (visits) for non-efficacy endpoints will average all records within each nominal visit.

3.2.4 Patient Populations Analyzed

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

Screened Patients is defined as those patients who signed an informed consent form.

Randomized Patients is defined as those screened patients who received a randomization assignment.

Safety Set (SS): All patients who are randomized and received at least 1 dose of Study Drug (ISIS 703802 or placebo). This population will be used for all safety analyses.

Full Analysis Set (FAS): All patients who are randomized and received at least 1 dose of Study Drug. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9. This population will be used for the analysis of efficacy.

Per Protocol Set (PPS): A subset of the FAS who have received within 6 months at least 22 weekly doses of Study Drug for patients randomized to Cohort A and at least 5 monthly doses of Study Drug for patients randomized to Cohorts B and C, and who have reported no major protocol deviations that

could compromise the interpretation of efficacy. Major deviations will be determined prior to unblinding for statistical analysis. This population will be used for supportive inferences concerning efficacy.

PK Population: All patients who are randomized and received at least 1 dose of ISIS 703802, and have at least 1 evaluable concentration result post first dose. This population will be used for analysis of PK data.

PK Subgroup: A subset of PK population who will have additional blood draws after dose administration on Day 1 and Week 26 (Cohort A) / Week 21 (Cohort B & C) to evaluate pharmacokinetic parameters.

3.2.5 Sample Size Considerations

Patients in the placebo arm will be pooled for the statistical analysis in order to compare each active treatment to the pooled control group. Therefore, each of the 4 treatment groups will have approximately 24 patients. Considering 10% dropouts, approximately 21 patients per group are expected to complete the study.
A sample size of 21 patients per arm will be able to detect:

- A treatment difference in mean triglycerides of 50% based on a between-patient standard deviation of 46% (Jani et al. 2014) and a two-sample t-test with an unadjusted alpha level of 0.05 with 93% power.
- A treatment difference in mean liver fat of 4.75% based on a between-patient standard deviation of 3.96% (Tiikkainen et al. 2004) and a two-sample t-test with an unadjusted alpha level of 0.05 with 96% power.

A total of approximately 96 patients (32 patients per cohort, including 24 patients per cohort treated with ISIS 703802) will be randomized to ensure that the efficacy of ISIS 703802 will be adequately characterized in the study.

3.2.6 Baseline and Endpoint Definition

For baseline platelet counts, all assessments from central and local labs will be used. For all other lab data, only values obtained from the central or reference lab will be used for baseline definition.

Baseline for triglycerides, ANGPTL3, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoC-III, ApoA-I, FFA, Lp(a), and other 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. 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.

Baseline for platelets is defined as the average of all central and local lab assessments combined prior to the first administration of Study Drug.

Baseline for ALT and AST is defined as the average of Day 1 pre-dose assessment and the last non-missing measurement prior to Day 1 pre-dose assessment.

Baseline for ECG is the average of the three ECG assessments taken on Day 1 Pre-dose for ECG. If only one or two ECG assessments are available, the single ECG assessment or average of the two ECG assessments will be used. If Day 1 Pre-dose ECG is missing, the averages of the ECGs obtained during the screening visit will be used as baseline.

Baseline for other measurements are defined as the last non-missing assessment prior to the first administration of Study Drug.

3.2.7 Patient Characteristics

Disposition and Protocol Deviations

Patient disposition, including reasons for premature discontinuation of treatment or follow-up, number of patients in Randomized Patients, SS, FAS, PPS, PK Population, and PK subgroup will be summarized for all screened patients. Listing of patient disposition will also be provided for Randomized Patients.

Major protocol deviations will be summarized by deviation category for Randomized Patients. All protocol deviations (major and minor) will be listed for Randomized Patients. Reasons for excluding patients from Per-Protocol Set will be summarized.

Demography and Baseline Characteristics

Patient demographic characteristics, including age (in years), sex, race, ethnicity will be summarized by treatment group for the FAS.

Baseline characteristics will include: weight (in kg) and weight by sex, height (in cm), BMI and BMI by sex, WHR, history of hepatic steatosis and years since diagnosis, history of confirmed type 2 diabetes mellitus and years since diagnosis, triglycerides, ANGPTL3, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoC-III, ApoA-I, FFA, Lp(a), HbA1c, HFF, VAT, SAT, biomarkers of inflammation (IL-6, TNF-a, IFN-g) and adipokines (as available), and will be summarized by treatment group for the FAS.

Previous medical history will be summarized by treatment group for the FAS.

Medication

All medications will be coded by World Health Organization Drug Dictionary (WHODrug, Version DEC2017). Missing or partial dates will be imputed as outlined below under conservative principles.

Missing or partial start dates:

- If year, month and day are all missing then assign the date of first administration of Study Drug
- If month and day are missing and year is:
  - earlier than the year of the first administration 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 administration of Study Drug then assign the last day of the month
- otherwise, assign the first day of the month

Imputation will be performed 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.

Imputed start and stop dates will be used to determine whether the medications are prior or concomitant to the treatment period. Prior medications include medications administered between the date of signed the informed consent and the first dose date, regardless whether continued while on treatment or not. A concomitant therapy is any drug or substance (including over-the-counter (OTC) medications, herbal medications and vitamin supplements) administered between first administration of Study Drug and patient's last contact date within the study. A prior medication with an imputed stop date that is missing or on or after date of first administration 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	≥ Inform Consent 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 DEC2017).

Prior and concomitant medications will be summarized separately by ATC class, preferred term, treatment group with counts and percentages, sorting by decreasing frequency in the All Patients

column. The concomitant medications in on-treatment and on-study period will be summarized respectively.

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. Original reported dates will be used for listings.

Treatment Exposure and Compliance

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall in Safety Set. Compliance to Study Drug will be summarized by descriptive statistics by treatment group and overall.

Treatment exposure in days will be calculated as date of last dose minus date of first dose +1 day.

Compliance (%) will be calculated as follows:

> 100 x (total volume of Study Drug) / (total volume of Study Drug scheduled during the treatment period).

For early withdrawals/terminations, the volume of Study Drug will be calculated for the period up to their withdrawal/termination.

3.3 Efficacy Analyses

Table 3 specifies efficacy analyses types, endpoint, population, statistical model and whether log-transformed data and multiple imputation are needed.

Table 3: Summary of Analysis Methods in Efficacy Analyses for Continuous Efficacy Endpoints

Endpoint	Analysis Type	Log-Transformed Data	MCMC imputation	Population	Model
Primary Endpoint	Primary analysis	Yes	Yes, assume MAR	FAS	ANCOVA
	Sensitivity Analysis 1	Yes	Yes, assume MAR	PPS	ANCOVA
	Sensitivity Analysis 2	Yes	Yes, assume MAR	FAS	non-parametric Wilcoxon Rank Sum test
	Sensitivity Analysis 3	Yes	Yes, assume MAR	PPS	non-parametric Wilcoxon Rank Sum test
	Sensitivity Analysis 4	Yes	Yes, Placebo: assume MAR. ISIS Treatment group:	FAS	ANCOVA

			Missing before discontinuation, assume MAR missing after discontinuation assume CIR		
	Sensitivity Analysis 5	Yes	No	FAS	ANCOVA
	Sensitivity Analysis 6	Yes	No	FAS	MMRM
	Subgroup analysis	Yes	Yes	FAS	ANCOVA
Secondary Endpoints: ANGPTL3 protein, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoC-III, ApoA-I, FFA, Lp(a)	Secondary analysis	Yes for Percent change from baseline; No for change from baseline	No	FAS and PPS	ANCOVA
Other Secondary Endpoints	Secondary analysis	No	No	FAS and PPS	ANCOVA
[redacted]	[redacted]	[redacted]	No	FAS	ANCOVA
LDL-C	Subgroup analysis	Yes for Percent change from baseline; No for change from baseline	No	FAS	ANCOVA

3.3.1 Primary Analyses

3.3.1.1 Primary Endpoint Definition

The primary endpoint is the percent change in fasting triglycerides from baseline to the primary analysis time point. The primary analysis time point is Week 27 for Cohort A, and Week 25 for Cohort B and C. Responses collected at these timepoints will be the endpoints considered in the primary efficacy analysis.

3.3.1.2 Primary Efficacy Analysis

The percent change from baseline in triglycerides will be analyzed using an ANCOVA model with treatment group as a fixed factor and log-transformed baseline triglycerides as a covariate. The ANCOVA model will use log(Y/base) as dependent variable, where Y is the post-baseline value of triglycerides and base is the baseline value of the triglyceride. The model will provide an estimate of the log ratio, which will then be converted back to the original ratio scale. The percent change from baseline will then be estimated based on the estimated ratio. Patients with missing primary endpoint will have their fasting triglyceride value imputed using the following multiple imputation method described below.

Missing data for the primary efficacy endpoint will be handled by a multiple imputation model that contains the following variables: log-transformed baseline fasting triglyceride value, log-transformed fasting post-baseline triglyceride values, stratified by treatment (Schafer 1997; Schafer 1999). Imputation of missing data will be conducted under a working assumption of missing at random (MAR), meaning that the propensity for a data point to be missing is not related to the missing data, but it is related to some of the observed data.

The imputations will be performed for post-baseline visits. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing primary endpoint by treatment group (ISIS 703802 treatment group or pooled placebo treatment group). In order to be compliant with the normality assumption, baseline and post-baseline triglyceride data will be log-transformed prior to the imputation process. Jeffreys' prior will be used to derive the posterior distribution of the parameters. The MCMC method will impute 100 datasets in order to estimate the treatment effect.

The primary endpoint will be compared between each ISIS 703802 treatment group and the pooled placebo group for each of the 100 imputed datasets. The estimates from the 100 fitted models will be combined to provide an overall estimate, with corresponding CIs and p-value (Little and Rubin, 2002). Results from the ANCOVA model will be tabulated by ISIS 703802 treatment groups compared to the pooled placebo group.

For fasting triglycerides, all observed values, change from baseline and percentage of change will be summarized by analysis visit using descriptive statistics in FAS.

Mean (SD) percent change over time in fasting triglycerides will be plotted by ISIS 703802 treatment group and pooled placebo group. Waterfall plots of by-patient percent changes from baseline to the primary analysis time point will also be provided.

The primary efficacy analysis will take place after the last patient has completed the primary analysis time point, and the database has been locked.

All primary efficacy data will be provided in data listings.

The primary efficacy analysis will be done using the FAS population.

The sample SAS code for the ANCOVA model can be found below: where the baseline and post-baseline values will be log-transformed first. Log (post-baseline/baseline) calculated as log (post-baseline) – log (baseline) will be subjected to the ANCOVA model.

```
**********************************************************************

* Note:
*  Base= baseline
 *  Y=Post-baseline
*  TRTP = Treatment group: pooled placebo, 40 mg Q4W, 80 mg Q4W, 20 mg QW
**********************************************************************

ods output lsmeans=lsm diffs=diff;

proc mixed data = dataset;

    class TRTP (ref='pooled placebo') ;

    model log (Y/base)= TRTP  log(Base) /solution cl;

    lsmeans TRTP/ diff cl;

run;
```

3.3.1.3 Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity Analysis 1 (PPS) – The primary efficacy analysis will be repeated, using the PPS population.

Sensitivity Analysis 2 and 3 (Non-Parametric Analyses) The primary efficacy endpoint will be analyzed using a non-parametric Wilcoxon Rank Sum test using both the FAS and the PPS. Missing data will be handled using the same MCMC multiple imputation method as the primary analysis. The treatment effect will be estimated using the Hodges-Lehmann estimator of the location shift between ISIS 703802 treatment groups and the pooled placebo group. Asymptotic 95% CI and corresponding p-values will be provided.

Sensitivity Analysis 4 (FAS) Using controlled imputations (pattern mixture models [PMM] with ANCOVA) will be conducted to assess the robustness of the missing at random assumption. With this approach, missing not at random (MNAR) is assumed, and the mean function for the missing data

from patients treated with ISIS 703802 who discontinue the study is pre-specified. Missing triglycerides for placebo patients will be imputed using the same MCMC multiple imputation method as the primary analysis. Patients treated with ISIS 703802 who discontinue the study due to AE or lack of efficacy will have their post-discontinuation Triglyceride values imputed using estimates from the placebo patients using the copy increment from reference (CIR) approach, detailed in (Carpenter et al. 2013). The assumption is based on the premise that when a patient discontinues treatment due to informative missing data, at the time of discontinuation they would progress in a similar manner as placebo-treated patients. Otherwise, non-informative missing data will be imputed using the same MCMC method as the primary analysis, since it is assumed that those patients would have continued in a similar manner to similar patients in their own treatment group who remained on the study. Therefore, the missing data for these patients is expected to be missing at random.

Sensitivity Analysis 5 (FAS) An ANCOVA will be performed on the primary efficacy endpoint (log-transformed) without applying any imputation for missing data.

Sensitivity Analysis 6 (FAS) A repeated measures analyses will be performed on the fasting triglyceride endpoint. The percent change from baseline in triglycerides will be analyzed using an MMRM model with treatment group as a fixed factor, log-transformed (if necessary) baseline triglycerides and timepoint as covariates. If log transformation is applied, the analysis will carry the same conditions as the primary efficacy analysis for back transformation. No imputation of data is applied to this analysis. Visit mapping is provided in Appendix A and SAS code is outlined in Appendix B.

3.3.2 Secondary Efficacy Analyses

All analyses of secondary endpoints will be performed on the FAS as primary and the PPS as supportive. Secondary efficacy analyses will be based on data collected at the primary analysis time point.

- Change and percent change from baseline at the primary analysis time point in ANGPTL3 protein, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoC-III, ApoA-I, FFA, Lp(a) will be compared between each ISIS 703802 group and pooled placebo group using an ANCOVA model without applying any imputation for missing data. In ANCOVA model, log(Y/X) will be dependent variable, where Y is the post-baseline lipid value and X is the baseline lipid value, log-transformed baseline will be a covariate.
- Change from baseline at the primary analysis time point in fasting plasma glucose, HbA1c, fasting insulin, HOMA-IR, fructosamine and glycated albumin will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate.
- Change and percent change from baseline at the primary analysis time point in weight, SBP and DBP will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate.
- Change and percent change from baseline at the primary analysis time point in hepatic fat fraction (HFF) by MRI-PDFF will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate.

- Proportion of patients reaching hepatic fat fraction (HFF) ≤ 8% and < 5% by MRI-PDFF at the primary analysis time point will be compared between each ISIS 703802 treatment group and pooled placebo group using a logistic regression model with baseline HFF as a covariate.
- Proportion of patients with percent decrease from baseline in hepatic fat fraction (HFF) by MRI-PDFF ≥ 30% and ≥ 25% at the primary analysis time point will be compared between each ISIS 703802 treatment group and pooled placebo group using a logistic regression model with baseline HFF as a covariate.
- Change from baseline at the primary analysis time point in Fatty Liver Index (FLI) will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate. Equation below will be used for FLI calculation:

$$FLI = \frac{(e^{0.953*\log e\,(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e\,(\text{ggt}) + 0.053*\text{waist circumference} - 15.745)}}{(1 + e^{0.953*\log e\,(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e\,(\text{ggt}) + 0.053*\text{waist circumference} - 15.745)}} \text{ X } 100$$

Note: Triglycerides in mg/dL; BMI in kg/m^2; GGT is Gamma-glutamyl-transferase in U/L; Waist circumference in cm.

- Change from baseline at the primary analysis time point in ALT and AST will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate.
- Change from baseline at the primary analysis time point in Adipokines and related metabolic markers such as leptin, adiponectin, and if available, phospholipids (e.g. ceramides, sphingolipids, diacylglycerol) will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate.
- Change from baseline at the primary analysis time point in body composition as measured by single slice MRI of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), waist circumference, WHR (waist-to-hip ratio), and BMI will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate.

Summary statistics including all observed values, change from baseline and percentage of change by visit will be performed for secondary efficacy endpoints on the FAS except parameters relevant for safety assessments (i.e., glycemic control, body weight, blood pressure, ALT and AST) that will be summarized on the SS.

[redacted]

[redacted]

3.3.4 Subgroup Analyses

Subgroup analyses will be conducted for primary efficacy endpoint in the FAS. Subgroups defined by the following will be evaluated:

- Sex (Male, Female)
- Use of triglyceride lowering drugs (fibrates, omega 3) (yes/ no)

Missing data will be handled using the same MCMC multiple imputation method and based on log-transformed data as the primary analysis.

A subgroup analysis of change and percent change from baseline in LDL-C at primary analysis time point will be performed in the FAS. Subgroups defined by the following will be evaluated:

- Statins use (yes/no)
- High/moderate intensity statins use (yes/no)

Table 4: Statin Intensity Classification (Stone NJ., et al, 2014)

	Intensity		
Statin (Preferred Term)	High	Moderate	Low
Atorvastatin	>= 40 mg	10 to <40 mg	<10 mg
Rosuvastatin	>= 20 mg	5 to <20 mg	<5 mg
Simvastatin	80 mg	20 to <80 mg	<20 mg
Pravastatin		>=40 mg	<40 mg
Lovastatin		>=40 mg	< 40 mg
Fluvastatin		80 mg	<80 mg
Pitavastatin		>= 2mg	< 2 mg

*Dose is total daily dose

3.4 Pharmacokinetic and Anti-Drug Antibody analysis

3.4.1 Pharmacokinetic Data Analysis

All PK data analysis will be conducted using the PK Population except the listing of PK concentrations which will be conducted on the Safety Set.

The concentrations of ISIS 703802 in plasma expressed as ISIS 703802-equivalent (as total full-length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 703802) will be summarized by nominal visit by treatment group with and without stratification by patient ADA status using descriptive statistics. In addition, plasma terminal elimination half-life of ISIS 703802 will be calculated using the post-treatment follow-up data if data permits.

Additionally, for patients in the PK subgroup only, PK parameters will be calculated using non-compartmental methods. The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) values will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve (AUC) values after the first dose ($AUC_{0\text{-}24h}$) and steady-state dose ($AUC_{0\text{-}24h}$ and AUC_{tau}) will be calculated using the linear trapezoidal rule. Other PK parameters may be calculated at the discretion of the Sponsor. Plasma PK parameters will be summarized using descriptive statistics with and without stratification by patient ADA status.

Exposure-response relationships between selected lipid and PK measures (e.g., plasma trough concentrations) may be explored in a separate population PK/PD analysis combined with other clinical studies.

3.4.2 Anti-Drug Antibody Data Analysis

All ADA data analysis will be conducted using the Safety Set.

The ADA of ISIS 703802 will be assessed before, during, and after treatment with Study Drug (ISIS 703802 or placebo). The ADA incidence will be summarized by nominal visit and at the patient level by treatment group, as the total number of and percent of evaluated patients with ADA negative, positive, and unknown status. Patient ADA status (positive, negative or unknown) for all evaluable patients, along with the study day associated with the first emergence of ADA positivity (i.e., onset of ADA), the last positive ADA status observed, and peak ADA titer will be listed by treatment group. Potential relationships of ADA with selected efficacy, safety, and PK measures may be evaluated.

3.5 Safety Analyses

All safety analyses will use the Safety Set unless otherwise specified. Unless noted otherwise, denominators for all tables will be number of patients in the SS. For visit based safety endpoints including laboratory assessments, vital signs, and ECG, the analyses will use nominal visit collected by CRF. Early termination visit will be treated as Week 25/Week 27 for summary table.

Most AE summary tables, lab shift and abnormality tables will be based on two sets of data: on-treatment and on-study. On-treatment period is from the first dose through one dosing interval post last dose. For cohort A (weekly dose), on-treatment period spans time from first dose to the last dose

+ 7 days; For cohort B&C (every 4-week dose), on-treatment period spans time from first dose to the last dose + 28 days. On-study period is from the first dose until the patient's last contact date within the study.

Safety endpoints include the following:

- Adverse events
- Clinical safety laboratory tests
- Vital signs
- ECG

3.5.1 Adverse Events

All adverse events will be coded by the MedDRA dictionary version 20.1. Missing or partial dates will be imputed as outlined as below under conservative principles:

Missing or partial start dates:
If year, month and day are all missing then assign the date of first administration of Study Drug

- If month and day are missing and year is:
  - the same as the year of the first administration of Study Drug then assign the month-day of first Study Drug
  - earlier than the year of the first administration of Study Drug then assign December 31
  - after the year of the first administration 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 administration of Study Drug then assign the day of first Study Drug
  - earlier than the month-year of the first administration of Study Drug then assign the last day of the month
  - after the month-year of the first administration of Study Drug then assign the first day of the month

Imputation will be performed 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.

AE summary tables will be based on two sets of data: on-treatment period and on-study period defined in section 3.5. Imputed AE start date and end date will be used to determine whether AE is on-treatment or on-study. On-treatment AE summary tables include all AEs with imputed start date or

imputed end date fall in on-treatment period. On-study AE summary tables include all AEs with imputed start date or imputed end date after first dose date.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that occurred after the first administration of Study Drug. An AE with a completely missing start date will be assumed to be treatment emergent. If the onset date/time is the same as or after the date/time of the first administration of Study Drug, then the event is considered to be treatment emergent. Note that imputed dates will be used for defining TEAEs.

Unless otherwise specified, the frequency of patients with any incidence of AEs and the number of events will be summarized by system organ class (SOC) and MedDRA preferred term (PT) for:

- TEAE
- TEAEs potentially related to Study Drug. Related is defined as "Related", "Possible", or missing relationship to Study Drug
- TEAEs by SOC, PT and 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
- Most common TEAEs by PT. Most common TEAEs are defined as an incidence of 10% or more within any treatment groups at preferred term level.
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent SAEs potentially related to Study Drug
- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death.

Summary tables will be sorted by decreasing frequency of SOC and then by decreasing frequency of PT within SOC in Pooled ISIS 703802 column. If frequency is same for different PTs, sort alphabetically. If SOC or PT is missing, show as "Not Coded" in table.

An overview of AEs will be provided for all TEAEs. Treatment-emergent AEs, treatment-emergent SAEs, TEAEs potentially related to Study Drug, TEAEs that lead to treatment discontinuation, treatment interruption, dose reduction, and death. Original CRF collected dates will be used for listings.

3.5.1.1 Treatment Emergent Adverse Events at Injection Site

Treatment-emergent AEs at injection site will follow two definitions:

Definition 1: Local cutaneous reactions at injection site (LCRIS) are defined as any AE with PT containing injection site erythema, injection site swelling, injection site pruritus, injection site pain, or injection site tenderness that started on the day of injection and persisted for at least two days (i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after injection). Events on the day of the injection with a missing resolution date are also included.

Definition 2: Injection Site Reactions (ISR) defined as any AE with PT or verbatim term containing 'Injection Site' that started on the day of injection and persisted for at least two days (i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after injection). Events on the day of the injection with a missing resolution date will also be included.

Treatment-emergent LCRIS will be summarized by SOC and PT and by severity on-treatment only. Treatment-emergent ISRs will be summarized by SOC and PT and by severity in on-treatment and on-study periods.

Additionally, the following will be summarized using Definition 2 (i.e., ISRs) for on-study period only:

- Percentage of injections leading to ISR for overall and preferred term will be summarized using descriptive statistics. Percentage of injections leading to ISR will be calculated as follows for each patient: (A/B) *100, where A = number of injections leading to ISR, and B = total number of injections.
- ISRs by injection location
- Incidence of ISR and time to first ISR

An additional table summarizing ISRs (Definition 2) on-treatment by SOC and PT and by severity within cohort will be presented.

3.5.1.2 Treatment Emergent Flu-Like Reactions (FLR)

Treatment Emergent Flu-Like Reactions (FLRs) will follow two definitions:

- **Definition 1**: TEAEs with either (i) influenza like illness or (ii) at least one of following PTs: pyrexia, feeling hot, or body temperature increased, plus at least two of the following PTs: chills, myalgia, and arthralgia, starting on the day of injection or the next day.

- **Definition 2**: TEAEs with following PTs or verbatim: influenza like illness, chills, myalgia, arthralgia, pyrexia, feeling hot, or body temperature increased, starting on the day of injection or the next day.

Note that imputed dates may be used for defining FLRs.

Treatment Emergent FLRs defined in Definition 1 will be summarized by category (i) or (ii). Treatment Emergent FLRs defined in Definition 2 will be summarized by SOC and PT. Both definitions will be presented for on-treatment.

Percentage of injections leading to FLRs (Definition 2) for overall and by preferred term will also be summarized using descriptive statistics. Percentage of injections leading to FLRs will be calculated for each patient as (A/B)*100, where A is the number of injections associated with FLRs, and B is the total number of injections.

3.5.1.3 Adverse Events of Special Interest

The TEAEs of bleeding based on the Haemorrhages (SMQ) Export from MedDRA version 20.1 will be summarized by SOC and PT and by severity in on-treatment and on-study period.

The TEAEs of bleeding in presence or absence of concomitant anti-thrombotic medication (ATC3 Text: Antithrombotic agents) will be summarized by SOC and PT in on-treatment period. The TEAEs of bleeding in presence or absence of concomitant antithrombotic medication will be listed as well.

An additional table summarizing treatment-emergent bleeding AEs on-treatment by SOC and PT within cohort will be presented.

3.5.2 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, glomerular filtration rate, uric acid, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, creatinine kinase, GGT, Cystatin-C
- Hematology: red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, white blood cells (WBCs), and WBC differential (percentage and absolute count), neutrophils, eosinophils, basophils, lymphocytes, and monocytes
- Coagulation: aPTT, PT, and international normalized ratio (INR)
- Test Performed at Screening Only: Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, FSH (women), serum βhCG (women), TSH, T3, T4. The screening test data will only be displayed in patient listings.
- Urinalysis: color, appearance, specific gravity, pH, protein, red blood cell, glucose, ketones, urobilinogen, glucose, bilirubin, leukocytes esterase, nitrate. For expanded urinalysis at certain visits, additional measurements will be performed including: microscopic examination, P/C ratio, A/C ratio.

- 24-hour Urine Test: creatinine clearance, protein and albumin. 24-hour Urine Test will only be displayed in patient listings.
- Renal Urine Biomarkers: NGAL, NAG and KIM-1
- Other assessments (glycemic control): plasma insulin, fasting plasma glucose, homeostatic model assessment of insulin resistance (HOMA-IR) as provided in the central laboratory data, proinsulin, C-peptide, fructosamine, glycated albumin, and glycated hemoglobin (HbA1c).
- Inflammatory Panel and Liver Biomarkers (apoptosis and fibrosis): hsCRP, IL-6, IFN gamma, TNF alpha, leptin, adiponectin, CK18 and PIIINP, and if available, ceramides, sphingolipids, and diacylglycerol (to be summarized as efficacy endpoints)

Note, additional tests may be requested for specific situations. They may be summarized and will be listed per rules below too. Additional laboratory tests for patients with platelet count <100,000/mm^3 will be listed.

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), i.e. outside the limit of quantification, will be converted to X (or limit of quantification) for the purpose of quantitative summaries. If urine albumin/creatine ratio (UACR) or urine protein/creatinine ratio (UPCR) is 'Cannot calc' indicating urine albumin or urine protein in the below quantification range, UACR and UPCR will be calculated as the ratio of urine albumin or urine protein to urine creatinine after converting urine albumin or urine protein to the limit of quantification. See Appendix C for details.

Estimated Glomerular Filtration Rate (eGFR) is based on the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation and is provided as a parameter in the central laboratory.

All laboratory test results will be listed. Separate listings will be provided for local and central labs. A separate listing for platelets will be provided that includes assessment from both local and central labs.

Chemistry, hematology, coagulation, other assessments and quantitative urinalysis (observed value, and change and percent change from baseline) will be summarized using descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum, mean 95% CI) by nominal study visit. Urinalysis dipstick protein will be summarized using frequency counts by nominal study visit. Lab summary table except for platelet count will be based on the scheduled visits in central lab data only with the results in original unit. Two sets of

summary tables will be provided for platelets. One is based on central lab data, the other is based on local lab data. Note baseline platelets uses both central and local in its calculation.

A confirmed laboratory value is based on consecutive lab values within 7 days (no matter central lab data or local lab data). If consecutive value is the same or worse, then the initial value is confirmed. If the consecutive value is better, then the initial value is confirmed using consecutive value category. In essence, when the consecutive value is better, the initial value is not confirmed. If there is no retest within 7 days then the initial value is presumed confirmed. If there are multiple results on the same day (no matter from the same lab vendor or different lab vendors), then the worst value will be utilized in the analysis.

The following lab results will be graded per Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Sept 2007). The incidence of shift from baseline to worst post-baseline value will be summarized for on-treatment and on-study periods. Post-baseline lab results are defined as any assessment taken after the first dose no matter central lab or local lab data. 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".

- 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
- BUN: shift from baseline to maximum post baseline value
- Creatinine: 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 by will be graded using the following criteria:

- ≥ 90 mL/min/1.73m^2
- ≥ 60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2
- ≥ 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2
- ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2
- < 15 mL/min/1.73m^2

Shift tables for eGFR, ALT, AST and total bilirubin will be provided using confirmed values as well.

The number and percent of patients who met a protocol-defined safety monitoring rule(s) and stopping rule(s) (see Protocol Section 8.6 for details) will be tabulated by treatment group. A listing

will be provided for patients who met protocol-defined safety monitoring rules and for patients who terminated treatment due to a protocol-defined stopping rule as well.

Additional investigation of hepatobiliary laboratory assessments, platelet counts and renal parameters will be performed for on-treatment and on-study periods as below.

Hepatobiliary Laboratory abnormalities: The number and percent of patients falling in each of the following category will be tabulated by treatment group:

- 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 > 3 x ULN - ≤ 5 x ULN
- ALT > 5 x ULN - ≤ 8 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 worst post-baseline assessments will be tabulated by treatment group and for pooled ISIS 703802.

- ALT/AST > 8 x ULN, which is confirmed
- ALT/AST > 5 x ULN, which is confirmed and persist for at least 2 weeks
- ALT/AST > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed and either:
    - Total bilirubin > 2 x ULN, or
    - INR > 1.5, or
    - Temporal association with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness (coded as abdominal pain or abdominal pain upper),, fever, rash or eosinophilia as a reported laboratory result > ULN; and where temporal will be defined as the report date of the confirmed laboratory parameter occurring within the interval of the associated adverse event start and stop dates.

For patients having confirmed 3-fold or greater elevations above the ULN for ALT or AST, a listing of all the ALT, AST, total bilirubin, INR, and alkaline phosphatase records will be provided.

Abnormalities of platelet counts: The number and percentage of patients falling in each of the following categories (using available central and local laboratory assessments) based on post-baseline assessments will be provided:

- Any 2 occurrences of platelet count < 140,000/mm^3
- Any single occurrence of platelet count < 100,000/mm^3
- Any 2 occurrences of platelet count < 140,000/mm^3 and any single occurrence of platelet count <100,000/mm^3

The nadir platelet count will be summarized by below categories:

- Decrease ≥ 30% of baseline
- Decrease ≥ 50% of baseline
- 100,000/mm^3 to < 140,000/mm^3
- 75,000/mm^3 to < 100,000/mm^3
- 50,000/mm^3 to < 75,000/mm^3
- 25,000/mm^3 to < 50,000/mm^3
- 0 to < 25,000/mm^3

All categories of abnormalities in platelet count will be provided using confirmed values for on-study period as well.

Abnormalities of renal function: The number and percentage of patients falling in each of the following categories based on confirmed worst post-baseline assessments will be provided:

- eGFR by CKD-EPI > 25% decrease from baseline
- eGFR (CKD-EPI) value < 45 mL/min/1.73 m^2
- urine albumin/creatinine ratio (UACR) > 165 mg/g (0.165 mg/mg)
- urine protein/creatinine ratio (UPCR) > 325 mg/g
- New onset hematuria defined as >=5 RBC/hpf (except for menstruating females)

3.5.3 Vital Signs Measurements

Vital signs will include blood pressure (SBP, DBP), body weight, body temperature, heart rate (HR), and respiratory rate (RR). Vital signs will be summarized using the descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum, mean 95% CI) for observed values, change from baseline, and percent change from baseline at each nominal study visit. Scheduled visit will be used for summary table.

3.5.4 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 the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, maximum, and mean 95% CI) of the results, as well as the change from baseline to each study visit, will be presented by treatment group in summary tables. Scheduled visit will be used for summary table.

The number and percent of patients who have the following reported events will be tabulated by treatment group and for pooled ISIS 703802.

- Absolute QT/QTcF/QTcB >450 msec
- Absolute QT/QTcF/QTcB >480 msec
- Absolute QT/QTcF/QTcB >500 msec
- Increase from baseline in QT/QTcF/QTcB >30 msec
- Increase from baseline in QT/QTcF/QTcB >60 msec
- Increase from baseline in PR ≥50% (if absolute baseline <200 msec)
- Increase from baseline in PR ≥25% (if absolute baseline >200 msec)
- Increase from baseline in QRS ≥50% (if absolute baseline <100 msec)
- Increase from baseline in QRS ≥25% (if absolute baseline >100 msec)

QTcB (msec) = QT (msec) / $(RR)^{1/2}$; if RR is missing, use QT (msec) * $(HR(bpm)/60)^{1/2}$

QTcF (msec) = QT (msec) / $(RR)^{1/3}$; if RR is missing, use QT (msec) * $(HR(bpm)/60)^{1/3}$

All the data collected in triplicate will be listed.

3.6 Interim Analysis

There is no interim analysis planned for the study.

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5 APPENDICES

Appendix A – Efficacy Measurement Analysis Visit Window

Lipids: Total Cholesterol (TC) , LDL cholesterol (LDL-C) , HDL cholesterol (HDL-C) , Non-HDL cholesterol (non-HDL-C), Triglycerides (TG), VLDL cholesterol (VLDL-C) , Lp(a), FFA, ApoB-48, ApoB-100, ApoB, ApoC-III, Apo A-I.

PD parameters: ANGPTL3, fasting insulin, HOMA-IR, Proinsulin, C-peptide, Fructosamine, Glycated albumin, Delipidated Free Glycerol, Fasting Plasma Glucose.

Phospholipids (if available): Ceramides, Sphingolipids, Diacyglycerol

Study Week	Target Day for Cohort A	Study Day Window for Cohort A	Target Day for Cohort B/C	Study Day Window for Cohort B/C
Screening	-35 to -8	≤ -8	-35 to -8	≤ -8
Qualification Visit	-7 to -1	-7 to < 1	-7 to -1	-7 to < 1
1	1	1	1	1
5	29	2 to 43	29	2 to 43
9	57	44 to 71	57	44 to 71
13	85	72 to 99	85	72 to 99
17	113	100 to 127	113	100 to 127
21	141	128 to 155	141	128 to 155
25	NA	NA	169	156 to 183
26	176	156 to 179	NA	NA
27	183	180 to 197	NA	NA
Follow up week 4	211	198 to 225	197	184 to 211
Follow up week 8	239	226 to 256	225	212 to 242
Follow up week 13	274	>256	260	>242

HbA1c, leptin, and adiponectin

Period week	Target Day for Cohort A	Study Day Window for Cohort A	Target Day for Cohort B/C	Study Day Window for Cohort B/C
Screening	-35 to -8	< 1	-35 to -8	< 1
1	1	1	1	1
13	85	55 to 115	85	55 to 115
25	NA	NA	169	139 to 199
27	183	153 to 213 for Cohort A	NA	NA
Follow up week 13		>213		>199

Hepatic fat fraction (HFF), SAT volume, VAT volume, SAT area, VAT area, VAT volume/SAT Volume ratio by MRI

Period week	**Target Day for Cohort A**	**Study Day Window for Cohort A**	**Target Day for Cohort B/C**	**Study Day Window for Cohort B/C**
Baseline	-12 to -1	<= 1	-12 to -1	<= 1
13	85	55 to 115	85	55 to 115
25	NA	NA	169	139 to 199
27	183	153 to 213	NA	NA

Record selection rules to identify analysis visit for use in efficacy analysis and summary tables is as follows:

Priority order for lipids, PD parameters, phospholipids and HbA1c is 1) Fasting records, 2) Nearest target day, 3) If equal distance (in days), choose the earlier one. 4) If on the same day, average of records

Priority order for other test is 1) Nearest target day, 2) If equal distance (in days), choose the earlier one. 3) If on the same day, average of records.

Appendix B – Repeated Measures Efficacy Visit Mapping Instructions for Sensitivity Analysis 6 and Model

For the MMRM analysis of Triglycerides we will be mapping per Appendix A for assignment to the analysis visits. For the MMRM we should only include the following analysis visit timepoints in the model: Week 5, 9, 13, 17, 21, PAT.

For the QW weekly treatment schedule include baseline, analysis visits week 5, 9, 13, 17, 21 and 27 where data in analysis visit 27 is mapped to a common visit to be used in both dosing schema, suggest week 100.

For Q4W treatment schedule include baseline, analysis visits week 5, 9, 13, 17, 21 and 25 where data in analysis visit 25 is mapped to a common visit to be used in both dosing schema, suggest week 100.

The sample SAS code for the repeated measures analysis can be found below:

```
**********************************************************************
* Note: Base = baseline                                              *
*       Y= post-baseline value at primary analysis time point
*       TRTP = Treatment group: pooled placebo, 40 mg Q4W, 80 mg Q4W, 20 mg QW
**********************************************************************
ods output lsmeans=lsm diffs=diff;
proc mixed data = dataset;
    class TRTP (ref='pooled placebo') avisit patient;
    model log(Y/base) = TRTP log(BASE) AVISIT AVISIT*TRTP
    repeated AVISIT / subject=patient (TRTP) type=un
run;
```

Appendix C – Below the Level of Quantification Instructions

When observing (due to urine albumin (<0.30 mg/dL) or urine protein (<4 mg/dL) levels falling below the detection limit) a result of "Cannot calc" for urine albumin/creatine ratio (UACR) or urine protein/creatinine ratio (UPCR) in the central laboratory data from Medpace, derive the UACR and UPCR assuming the worst case for urine albumin and urine protein (hence the highest values). This would mean setting the below detection albumin and protein results to the detection limit by dropping the '<' sign and dividing by urine creatinine.

For example: In the LAB data, LABTYPE = 'Urinalysis':

> If LABTEST = 'P/C Ratio (Urine Protein/Urine Creatinine)' and RESULTC='Cannot calc', set 'Protein, quantitative' to 4 and compute UPCR (mg/mg) as "Protein, quantitative (mg/dL) divided by Urine Creatinine (mg/dL)".
>
> If LABTEST = 'Albumin/Creatinine Ratio' and RESULTC='Cannot calc', set 'Urine Albumin' to 0.3 and compute UACR (mg/g) as "1000 x Urine Albumin (mg/dL) divided by Urine Creatinine (mg/dL)".