Official Title:	**ISIS 304801-CS7 The APPROACH Open Label Study Volanesorsen (ISIS 304801) An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)**
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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 304801-CS7

The APPROACH Open-Label Study

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Date: 28 March 2019

Version: 3.0

Statistical Analysis Plan Signature Page

Akcea Therapeutics, Inc.

22 Boston Wharf Road, ,9th Floor

Boston, MA 02210

Compound Name: Volanesorsen (formerly ISIS 304801)

Protocol: ISIS 304801-CS7

Study Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Issue Date: Protocol Amendment 8 – 21 November 2018;
Protocol Amendment 9 - France – 25 May 2018

Signature: [redacted] Date: 29 MAR 2019

[redacted] M.D., M.S.

[redacted]

Ionis Pharmaceuticals, Inc.

Signature: [redacted] Date: 29 Mar 2019

[redacted] Ph.D.

[redacted]

Ionis Pharmaceuticals, Inc.

[redacted]

Ionis Pharmaceuticals, Inc.

Signature: [redacted] Date: 29 Mar 2019

[redacted] Ph.D.

[redacted]

Ionis Pharmaceuticals, Inc.

Signature: _____ Date: _____

[redacted] Ph.D.

[redacted]

Akcea Therapeutics, Inc.

Signature: _____ Date: _____

[redacted] Ph.D.

[redacted]

Ionis Pharmaceuticals, Inc.

Signature: [redacted] Date: 29 MAR 2019

[redacted] Ph.D.

[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]
Biostatistics Reviewer	[redacted] Project Role: [redacted]
Statistical Programming Reviewer	[redacted] Project Role: [redacted]

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SUMMARY OF CHANGES

The following major modifications have been made to ISIS 304801 CS7 SAP, version 3.0, dated 25 MAR 2019.

List of Modifications

Section	Title	Change/Rationale
2.1	General Overview of Procedures	Add extended treatment period
3.2.1	Statistical Methods	Change Study Day Window for Abdominal Pain screening period from “Screening” to “Week -1”, “Week “-2”, etc. Correct Abdominal Pain Week 1 study day window from "1" to "1 to - 3"; Add MRI mapped visits and study day windows Add patient year of exposure as used in AdHoc analysis Update Study Day Window for Fasting Lipid Assessment Week 52 and Week 64 to be taking the midpoint of next visit which is consistent with visit windows for other visits. Add Study Day Window week 78, 117, 130 for Quality of Life Assessments (EQ-5D, SF-36) – France per protocol Amendment 9 -France Add fasting lipid assessment week 117 and week 130 (France) study day window
3.2.2	Patient Population Analyzed	Removed per-protocol set. The first 13 week dosing compliance will not bring much value for the long term efficacy in this long-term extension open label study.
3.2.3	Baselines and Other Definition	QOL: remove “Pre-dose” from definition 12-lead ECG: Remove “(4 weeks)” from definition MRI: clarify MRI baseline definition as “last non-missing assessment on or prior to Study Day 14 of volanesorsen in index studies or Open-label study”
3.2.4	Patient Baseline data, Medical history and Disposition	Add description of AdHoc summaries: • Disposition through Studies CS6 and CS7 • Disposition/number of patients by month through index and open-label study • Discontinuation Rate in the index studies and open-label study overall • Kaplan Meier Plot of Treatment Continuation

Section	Title	Change/Rationale
3.3	Efficacy Analysis	Add description of AdHoc summaries: • Summary and by patient listing of dosing, TG, platelet, pancreatitis, and abdominal pain • By age group summaries • Pancreatitis incidence rate per patient year
3.3.5	Frequency and severity of patient reported abdominal pain	Change "treatment period" to "on-treatment period" Add description of AdHoc summaries: • Summary for CS6 subjects who roll-over to CS7 • Summary and figure for patients with pain at baseline in CS6 subjects who roll-over to CS7 • Patient profile figures
3.3.9	Adjudicated acute pancreatitis events Rate	Add patient reported moderate or severe abdominal pain (pain score: 4-10) in the planned summary. Add description of AdHoc summaries: pancreatitis incidence rate per patient year of exposure
3.5	Safety Analyses	On-Study period was updated from "the first dose of the Study Drug to end of the study" to "**Day 1 of volanesorsen** to end of the study" On-treatment period was updated from "the first dose of the study medication to the last dose of study medication + 28 days." to "the first dose of volanesorsen to the last dose of volanesorsen + 28 days."
3.5.2.1	General Analysis of AEs	Add description of AdHoc summaries: 1. Summary of on-study AEs by treatment and age for FCS patients and all patients in safety set 2. Summary of treatment emergent renal adverse events
3.5.2.3	Other Events of Interest	Add description of Platelet Count Decreased/ Thrombocytopenia Events from AdHoc summary Add below description of additional analysis in AdHoc request: "The frequency of patients with any incidence of AEs and the number of events will be summarized by MedDRA preferred term (and severity) sorted by frequency for: 1. Any treatment emergent bleeding AEs for the safety set, for the subset of patients on concomitant anti-coagulant or anti-platelet medication, and for the subset of patients not on concomitant anti-coagulant or anti-platelet medication. 2. Treatment emergent bleeding AEs under

Section	Title	Change/Rationale
		contemporaneous use of concomitant anti-coagulant or anti-platelet medication for the subset of patients on concomitant anti-coagulant or anti-platelet medication. Treatment emergent bleeding adverse events will be listed. In addition, treatment emergent bleeding adverse events will be listed by platelet count categories before and after bleeding, and anti-platelet or anti-coagulant medication." Add description of additional analysis in post-submission request: 1. Revised LCRIS 2. Discoloration AE Add Revised FLRs definition
3.5.4.2	Additional analyses of key safety laboratory data	Add below description of additional analysis in AdHoc request: "The incidence of patients with post-baseline platelet results falling in each of the following categories will be summarized for the safety set and the subset of patients with normal baseline ($\geq$140,000/mm^3): • With >= 2 consecutive values of platelet count < 140,000/mm3 • With platelet count <100,000/mm3 at final visit • With >= 2 consecutive values of platelet count < 140,000/mm3 or with platelet count <100,000/mm3 at final visit Summary figures will be generated for platelet counts over time (absolute values, absolute change from baseline, and percent change from baseline) in patients treated with placebo in ISIS 304801-CS6 who then treated with Volanesorsen in ISIS 304801-CS7. The incidence of patients with post-baseline platelet results falling in each of the following categories will be summarized for the safety set: • Any serum creatinine >=0.3 mg/dL higher than baseline • Any serum creatinine >=50% higher than baseline • Final visit serum creatinine >=0.3 mg/dL higher than baseline • Final visit serum creatinine >=50% higher than

Section	Title	Change/Rationale
		baseline" Add below description of additional analysis in post-submission request: "hsCRP will be classified to Normal or > Upper limit of normal (ULN), and the incidence rate of shift from safety baseline to maximum post-baseline category will be summarized." Add coagulation assessments shift table based on the toxicity grade Add summary of platelet count (any occurrence/nadir value) Add ratio of post-baseline central (and local) lab platelet test numbers to total number of injections Add time to recover from platelet values Add summary figure (overall and by age group) for platelet count over time Add scatter plot for nadir platelet counts vs. selected factors Add summary table and figure of selected hematology/urinalysis/normalized urinary creatinine assessments Add shift tables for urine albumin/creatinine ratio and urine protein/creatinine ratio Add listing for patients with ALT or AST > 3 x ULN
3.5.5	Exposure	Updated to add dose adjustment, dose interruption/pauses; and remove amount of Study Drug in mg from the description of exposure summaries Add treatment duration in months during index study and open-label study description per request in post-submission. Add summary of dose interruption/reduction, number of dose pauses and missed dose per patient year of exposure.

Section	Title	Change/Rationale
3.5.9	Concomitant Medications	Update WHODrug version from Dec 2014 to Sep 2016; Add below description of additional analysis in AdHoc request: "Concomitant anti-coagulant and anti-platelet medications will also be summarized for the Safety Set by decreasing frequency in the overall column."

ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alanine Phosphatase
ALT	Alanine Aminotransferase
apo	Apolipoprotein
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
Cmax	Maximum Observed Drug Concentration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
ET	Early Termination
FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
FLRs	Flu-like Reactions
GLP-1	Glucagon-like Peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein Cholesterol
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Immunogenicity
INR	International Normalized Ratio
IRB	Institutional Review Board
LCRIS	Local Cutaneous Reaction at Injection Site
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol

LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model for Repeated Measures
MRT	Mean Residence Time
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
PD	Pharmacodynamic
PK	Pharmacokinetics
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
Tmax	Time to Maximal Concentration
TG	Triglyceride
ULN	Upper Limit of Normality
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very Low-Density Lipoprotein Cholesterol

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 304801-CS7. 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 deviation from the final version of the Statistical Analysis Plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

1.1 Study Overview

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks in the CS7 study.

Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period.

There is no primary efficacy endpoint. Both efficacy endpoints and safety endpoints will be summarized to evaluate the safety and efficacy of extended dosing with volanesorsen sodium 300 mg in patients with FCS.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed.

Patients will be enrolled into the treatment phase of the study after all Screening (Group 3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in protocol Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

1.2 Objectives

To evaluate the safety and efficacy of dosing and extended dosing with ISIS 304801 (volanesorsen sodium 300 mg) in patients with FCS.

1.3 Hypotheses

There is no formal study hypothesis. Hypothesis tests for efficacy endpoints will be done for exploratory purposes.

1.4 Endpoints

For fasting lipid measurements including TG, total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, LDL-C, and total apolipoprotein C-III :

The values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments,

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

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

1.4.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG,
- Frequency and severity of patient reported abdominal pain during the on-treatment period,
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C,
- Percent change from baseline in fasting total apolipoprotein C-III,
- Change from baseline in Quality of Life (QOL) questionnaires (EQ-5D, SF-36),
- Independently adjudicated acute pancreatitis event rate,
- Frequency of other symptoms: eruptive xanthoma, lipemia retinalis.

1.4.2 Safety Endpoints

- Number and percentage of patients reporting AEs including independently adjudicated events of pancreatitis and major acute cardiovascular events (MACE), local cutaneous reactions at injection site, flu-like reactions, and platelet reduction,
- Change from baseline in vital signs and weight,
- Change in physical examinations findings,

- Change from baseline in clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis),
- Chang in echocardiography findings,
- 12-Lead electrocardiograms (ECGs) results,
- Use of concomitant medications, and
- Change from baseline in MRIs.

2 PROCEDURES

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

- Screening/Qualification:
- Qualification of Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor).
- Screening and Qualification of Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks.
- A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
- Option to participate in an extended treatment period (up to an additional 52 weeks)
- A 13-week post-treatment evaluation period

2.1 General Overview of Procedures

2.1.1 Screening/Qualification

Group 1 and 2 patients (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

2.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 10 times during Weeks 1-52 (see Schedule of Procedures in Appendix A of the protocol). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety

reasons. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma trough concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and QOL assessments will be performed according to the schedule of procedures in Appendix A of the protocol. AEs at the injection site should be collected as AEs. Dietary counseling will commence at the start of the diet stabilization period and will be reinforced at intervals throughout the treatment and follow-up period. All blood and urine samples should be collected prior to Study Drug administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42 44, 46, 48, and 50 may be conducted by a home healthcare nurse . Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

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.

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Section 8.6.3 of the protocol for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

2.1.3 Extended Treatment Period

Patients will have the option of continuing treatment for up to an additional 52 weeks until an expanded access program is approved and available in their country.

During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A of the protocol). Study Drug will be administered once weekly unless the patient is on a biweekly treatment schedule for safety reasons. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should

be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Treatment instructions and training will be provided to the patient where applicable.

2.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C of the protocol.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A of the protocol.

2.1.5 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period. This 13-week post-treatment evaluation period consists of 4 Study Center visits on Weeks 54, 56, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A of the protocol. Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 4 Study Center visits on Weeks 106, 108, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A of the protocol.

2.2 Randomization & Treatment Allocation

This is an open-label study to the Phase 3 study of rolled over volanesorsen patients with FCS (ISIS 304801-CS6 or ISIS 304801-CS16) and newly-enrolled patients who did not participate in the index studies. All patients will initiate treatment with volanesorsen 300mg by SC injection weekly and continue on this dose and regimen unless they meet a per-protocol dose adjustment criterion.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice 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 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 before index study completion, 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 8.5.5.

For the purpose of pre-programming and data cleaning, PAREXEL unblind programming team (the CRO performing the statistical analysis) and an independent data manager at Medpace Laboratories will receive post-baseline lipid panel results.

2.5 Data Management

The following is applied to all index studies (ISIS 304801-CS6 or ISIS 304801-CS16) and all 3 groups in this open-label study.

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. The Sponsor 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 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 is responsible for the review of the clinical laboratory data. This data is not stored in the EDC system. Investigator sites have access to the data via printed lab reports sent directly from the laboratory.

2.5.3 Pharmacokinetics (PK) Data

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

2.5.4 Other Data

Bracket is the eDiary vendor that contains abdominal pain and QoL assessments. Medpace Imaging Central Lab manages MRI, ECHO, and Fundus photography. Blood Center of Wisconsin manages antiplatelet antibodies and anti-PF4 assay data. Quest Pharmaceutical Service manages anti-volanesorsen antibody assessment. University of Western Ontario ([redacted]Professor [redacted]) manages genetic sequencing data. These data will also not be stored in the EDC system but will be transferred to the Sponsor as external data.

2.5.5 Adverse Events Adjudication

[redacted] 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.

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. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be independently adjudicated.

3 ANALYSIS PLAN

3.1 Statistical Design Summary

This is a multi-center open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Group 1 and Group 2 patients who complete one of the index studies and who are qualified plus Group 3 patients who are screened and qualified will be enrolled to this open-label study. The safety and efficacy of extended dosing with volanesorsen in patients with FCS will be evaluated by summary tables rather than hypothesis tests. Missing data will not be imputed.

3.1.2 Sample Size Consideration

No sample size calculations were performed as this is an open-label extension study.

3.1.3 Planned Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded.

Planned summaries and patient data listings for disposition, demographic, efficacy and safety will be included in this interim analysis.

Additional interim analyses will be performed to support regulatory filing activities.

3.2 General Overview of Analyses

3.2.1 Statistical Methods

All eCRF 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 enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables.

Efficacy data including fasting lipid measurements, abdominal pain and QOL results will be mapped to analysis visit specified in the table below.

The intent of these 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 efficacy assessments, then those assessments collected at Early Termination visit and during post-treatment follow-up period should be mapped to analysis visits as well. If there are multiple assessments within a visit window, only scheduled visit will be used. If there are multiple scheduled assessments, for fasting lipid measurements and numeric QOL results, average will be used; for abdominal pain and character QOL results, the worst will be used. If the assessments are all unscheduled, the visit nearest the scheduled date will be used unless two visits are equally near, in which case the average will be used. For fasting lipid 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.

Efficacy/PD measure	Mapped Visit (Week)	Target	Study Day Window
Fasting Lipid Assessment	Screening	-56 to -15	≤-15
	Qual Visit	-14 to -7	-14 to <1
	1	1	1
	4	22	2 to 36
	8	50	37 to 64
	12	78	65 to 82
	13	85	83 to 106
	25	169	107 to 173
	26	176	174 to 197
	38	260	198 to 302
	50	344	303 to 351
	52	358	352 to 400
	extended treatment period		
	64	442	401 to 484
	76	526	485 to 575
	90	624	576 to 673
	104	722	674 to 743
	117	813	744 to 858
	130 (France)	904	859 to 949
Abdominal Pain			
	m	n×7+1	mx7+3 to mx7-3, m = -1, -2, …
	…		
	-2	-13	-11 to -17
	-1	-6	-4 to -10
	1	1	1 to -3
	2	8	5 to 11

	3	15	12 to 18
	n	(n-1) ×7+1	(n-1)×7-2 to (n-1) ×7+4
	…		
MRI			
	Screening	NA	≤ 14
	52	358	298 to 418
Quality of Life Assessments (EQ-5D, SF-36)			
	1	1	1
	13	85	55 to 115
	26	176	146 to 206
	52	358	328 to 404
	65	449	405 to 479
	78 (France)	540	496 to 570
	117 (France)	813	769 to 843
	130 (France)	904	860 to 934

Note: Regarding lipid measurements for efficacy analyses, mapped observed assessments defined in this table will be derived further. The derivations for baselines are described in section 3.2.3. The derivations for Month 3, 6 and 12 are described in section 3.3.1.

Non-efficacy by visit assessments will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged.

Unscheduled results and data from local labs will not be included in the by visit summaries but will be used in the determination of baseline, in the laboratory abnormality, stopping rule, and platelets reduction analyses presented in data listings.

Unscheduled results from the central lab will be used in the determination of baseline, laboratory abnormality summaries, and shift from **safety baseline** to worst post-baseline, and platelets reduction analyses only, and presented in data listings. Local lab data will be only used in platelet analyses (including by visit summaries, abnormality summary, shift from Baseline to worst post-baseline, reduction analyses), and presented in data listings.

Summary tables and figures will NOT be presented by the treatment group in each index study (ISIS 304801-CS6 or ISIS 304801-CS16) and the newly enrolled patients as a separate group per protocol. Per Sponsor decision, most summary tables and figures will be presented in the following groups, i.e. Treatment naive group, CS6-Volanesorsen, CS16-Volanesorsen, and Overall, if applicable.

Note: “Treatment naive group” for most tables and figures is a combined group of subjects including CS7-New, CS6-Placebo and CS16-Placebo. When the summary is based on **Index Study Baseline**, “Treatment naive group” is a combined group of subjects including CS6-Placebo and CS16-Placebo.

Summary tables for PK concentration and IM data will be presented by Treatment naive group, CS6-Volanesorsen, CS16-Volanesorsen, and Volanesorsen combined (i.e., CS6-Volanesorsen and CS16-Volanesorsen combined). Summary figures for PK concentration data and summary tables for PK parameters will be presented by Treatment naive group and Volanesorsen combined.

Total patient year of exposure will be calculated as summation of [minimum (latest visit date, data cutoff date) – treatment start date +1]/365.25 for all subjects.

For listings, data will be displayed as an order of following:

- Treatment naive group: CS7-New
- Treatment naive group: CS6-Placebo
- Treatment naive group: CS16-Placebo
- CS6-Volanesorsen
- CS16-Volanesorsen

3.2.2 Patient Population Analyzed

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

Full Analysis Set (FAS): All patients who are enrolled and received at least one dose of Study Drug and who have an open-label study baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

The significant deviation criteria are listed in Appendix A.

All protocol deviations will be listed in the patient data listings.

Safety Set: All patients who are enrolled and receive at least one dose of Study Drug. Group 1 and Group 2 patients will be summarized in the actual treatment group patients received during index study. Patients randomized to receive placebo in the index study, incorrectly treated with volanesorsen during the index study treatment period will be counted in the volanesorsen group from the first dose of volanesorsen received.

PK Population: All patients who are enrolled and receive at least one dose of Study Drug, and have at least one post first dose PK sample collected, analyzed, and not excluded by PK scientist as the PK result was considered to be an outlier. Group 1 and Group 2 patients will be summarized in the actual treatment group patients received during index study. Patients randomized to receive placebo in the index study, incorrectly treated with volanesorsen during the index study treatment period will be counted in the volanesorsen group from the first dose of volanesorsen received. Group 3 patients will be summarized under Treatment naive group.

All efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

Analysis populations will be summarized with counts and percentages by the group presented in Section 3.2.1.

3.2.3 Baselines and Other Definition

Baselines for fasting lipid measurement:

Definitions of baselines, including the **Index Study Baseline** (for Group 1 and Group 2 only) and the **Open-label Study Baseline** (for Group 1, 2, and 3) , are given below for the purposes of the final analysis.

- **Index Study Baseline** for Group 1 and 2 is defined as the average of Index Study Day 1 pre-dose assessment and the last measurement prior to Index Study Day 1 pre-dose assessment. If one of the two 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.
- **Open-label Study Baseline** for Group 1, 2 and 3 is defined as the average of open-label Day 1 pre-dose assessment and the last measurement prior to open-label Day 1. If one of the two 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.

Baselines for QOL (EQ-5D, SF-36):

1. **Index Study Baseline** for Group 1 is defined as the last non-missing assessment on Week 1 of treatment, volanesorsen or Placebo, in index studies.
2. **Open-label Study Baseline** for Group 1, 2 and 3 is defined as the last non-missing assessment on Week 1 in this Open-label study.

Baselines for patient reported abdominal pain:

1. The average of maximum intensity:
2. **Index Study Baseline** for Group 1 is defined as the average of maximum intensity during the screening period and Week 1 in index studies.
3. **Open-label Study Baseline** for Group 1, 2 and 3 is defined as the average of maximum intensity within 4 weeks (including week 1) prior to Day 1 of treatment in this open-label study.
4. The worst of maximum intensity:
5. **Index Study Baseline** for Group 1 is defined as the worst of maximum intensity during the screening period and Week 1 in index studies.
6. **Open-label Study Baseline** for Group 1, 2 and 3 is defined as the worst of maximum intensity within 4 weeks (including week 1) prior to Day 1 of treatment in this open-label study.

Safety Baseline for Platelet count: is defined as the average of all available measurements, including central lab measurements and local lab measurements, prior to Day 1 of volanesorsen, i.e.

1. For subjects in Group 1 and 2 who were treated with volanesorsen in the index study, it is all available measurements prior to Day 1 of treatment in index study
2. For subjects in Group 3, it is all available measurements prior to Day 1 of treatment in this Open-label study

3. For subjects in Group 1 and 2 who were treated as placebo in the index study, it is all available measurements within 4 weeks prior to Day 1 of volanesorsen in this open-label study.

Safety Baselines for 12-lead ECG: is defined as the average of the triplicate ECGs taken on screening visit of this Open-label study or the last visit in the parent study, if only one or two assessments are available, the single assessment or average of the two assessments will be used.

4. For subjects in Group 1 and 2 who were treated as volanesorsen in the index study, it is the last visit prior to Day 1 of treatment in index study

5. For subjects in Group 3 and subjects in Group 1 and 2 who were treated as placebo in the index study, it is the last visit prior to Day 1 of treatment in this Open-label study

Safety Baselines for vital sign, clinical safety lab (except for the platelet) and MRI

It is defined as last non-missing assessment prior to Study Day 1 pre-dose of volanesorsen in index studies or Open-label study.

Safety Baselines for MRI: is defined as last non-missing assessment on or prior to Study Day 14 of volanesorsen in index studies or Open-label study.

Baselines for analyses:

- Efficacy analyses are based on the **Index study Baseline** and the **Open-label study Baseline**. Details of separate analyses based on each baseline will be specified in the section 3.3.
- Safety analyses are based on **Safety Baseline**. Details of separate analyses based on each baseline will be specified in the section 3.5.

3.2.4 Patient Baseline data, Medical history and Disposition

Summary tables in this section will be presented for the FAS by the group presented in Section 3.2.1.

Baseline data (demographic, disease history and baseline disease characteristics) will be summarized. It will also be displayed in the patient data listings.

- Demographic including age, gender, ethnicity, race, weight and BMI will be summarized using descriptive statistics by the group presented in Section 3.2.1. Age is calculated by using the informed consent date of the open-label study and birth date. Gender, ethnicity and race for Group 1 and 2 patients were collected in each index study.
- Disease history includes duration of FCS diagnosis at screening, age at FCS diagnosis, lipemia retinalis, eruptive xanthomas history, pancreatitis history, glybera treatment history, confirmation for known loss-of-function mutations in Type 1-causing genes, documentation of post heparin plasma LPL activity <=20% of normal based on medical history, confirmation for type 1 phenotype based on genetic sequencing results, post heparin plasma LPL activity <=20% of normal based on lab results, , and history of type II diabetes.

- Baseline disease characteristics includes: body weight, height at Day 1 of the Open-label study, Body Mass Index (BMI) , fasting lipids results including TG, LDL-C, HDL-C, Total Cholesterol, non-HDL-C, VLDL-C, apoA-1, apoB and apoC-III.

Medical history collected in the open-label study 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 for the Safety Set. Medical history will also be provided in the patient data listings.

Patient disposition of the open-label study will be summarized for all enrolled patients. The number of patients enrolled, dosed, completed treatment, along with reasons for discontinuing treatment and withdrawing from the study, completed post-treatment follow-up, along with reasons for early terminating post-treatment follow-up, will be presented. Patient disposition through CS6 and CS7 will also be summarized.

Treatment discontinuation by month will be presented through index studies and open-label study to present number of patients discontinued in each study month and corresponding discontinuation reason, and remaining number of patients in the study.

Summary of discontinuation rate per patient year of exposure in the index studies and open-label study overall will be generated.

Kaplan Meier Plot of Treatment Continuation will be provided for below comparisons:

- CS6 volanesorsen arm vs CS7 treatment naive group in patients with history of pancreatitis
- CS6 volanesorsen arm vs CS7 treatment naive group in patients with history of pancreatitis through Month 12
- CS6 volanesorsen arm vs CS7 treatment naive group in safety set through Month 12

Listing of patient disposition will also be provided.

3.3 Efficacy Analysis

Efficacy endpoints include: percent change and change in fasting lipid measurements, frequency and severity of patient reported abdominal pain, change from baseline in QOL, adjudicated acute pancreatitis events rate and frequency of other symptoms.

Efficacy analyses will be conducted in the FAS by the group presented in Section 3.2.1.

For fasting lipid measurements and QOL (EQ-5D, SF-36), both the **Index Study Baseline** and the **Open-label Study Baseline** will be used. In the summary tables using the **Open-label Study Baseline**, visits are mapped to analysis visits as shown in Section 3.2.1 for fasting lipid measurements and QOL (EQ-5D, SF-36) in the open-label study. In the summary tables using the **Index Study Baseline**, visits include the index study baseline visit, and the open-label study mapped post baseline visits.

Efficacy analyses for the fasting TG will be performed on FAS.

By patient listings will have all efficacy endpoints results collected in the open-label study.

Summary table and by patient listing will be generated by visit window, dose level, fasting TG and corresponding change from baseline value, nadir platelet, any pre-treatment adjudicated pancreatitis events, and abdominal pain event (average of intensity and yearly rate of frequency of moderate or severe events). Below visit windows will be utilized:

Visit Window	Dose Level	TG	Platelet Nadir	Abdominal Pain
0-3 months	week 1-13	month 3	day 1-91	week 2-14
3-6 months	week 14-26	month 6	day 92-182	week 15-27
6-9 months	week 27-39	week 38	day 183-273	week 28-40
9-12 months	week 40-52	month 12	day 274-364	week 41-53
12-15 months	week 53-65	week 64	day 365-455	week 54-66
15-18 months	week 66-78	week 76	day 456-546	week 67-79
18-21 months	week 79-91	week 90	day 547-637	week 80-92
21-24 months	week 92-104	week 104	day 638-728	week 93-105
24-27 months	week 105-117	week 117	day 729-819	week 106-118

3.3.2 Percent change and absolute change from baseline in fasting TG

The Month 3 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. If one visit is missing, then the other visit will be used as the 3-month endpoint. If both visits are missing, then the 3-month endpoint will be set as missing.

The Month 6 analysis time point is at the end of Month 6 where the value 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 as the 6-month endpoint. If both visits are missing, then the 6-month endpoint will be set as missing.

The Month 12 analysis time point is at the end of Month 12 where the value 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 as the 12-month endpoint. If both visits are missing, then the 12-month endpoint will be set as missing.

Percent change and absolute change from the **Open-label Study Baseline** at Month 3, Month 6, and Month 12 in this open label study, and percent change and absolute change from the **Index Study Baseline** in fasting TG at index study Month 3, Month 6, and Month 12, and the open label study Month 3, Month 6, and Month 12 will be summarized. For patients enrolled to extended treatment period, percent change and absolute change from the **Open-label Study Baseline** and percent change and absolute change from the **Index Study Baseline** in fasting TG at Week 64, 76, 90, and 104 will also be summarized.

These analyses will be repeated using on-treatment period data, which is defined as the last dose date of study medication + 28 days.

A descriptive summary of TG over time will be conducted overall and by age group (<65 years vs. >=65 years). A descriptive summary of TG over time during on-treatment period will also be conducted overall.

3.3.3 Treatment response rates

Treatment response rate, where patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized overall and by age group (<65 years vs. >=65 years). Four response rates are defined as following:

- Response rate 1 is defined as the proportion of patients with fasting plasma TG < 750 mg/dL at Month 3, Month 6, or Month 12 in the subset of patients with the **Open-label Study Baseline** fasting plasma TG ≥ 750 mg/dL.
- Response rate 2 is defined as the proportion of patients with fasting plasma TG < 750 mg/dL at Month 3, Month 6, or Month 12 in the subset of patients with the **Index Study Baseline** fasting plasma TG ≥ 750 mg/dL.
- Response rate 3 is defined as the proportion of patients who achieve fasting TG ≥ 40% reduction from the **Open-label Study Baseline** at Month 3, Month 6, or Month 12 for all patients with both baseline and post baseline results.
- Response rate 4 is defined as the proportion of patients who achieve fasting TG ≥ 40% reduction from the **Index Study Baseline** at Month 3, Month 6, or Month 12 for all patients with both baseline and post baseline results.

Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

- Response rate 1 and 2 will also be conducted by using other response thresholds (e.g., 500, 880, 1000 mg/dL).
- Response rate 3 and 4 will also be conducted by using other response thresholds (e.g., ≥ 20%, 30%, 50%, 60%, 70% reduction).

Patients with both baseline and post baseline results will be included in the summary and counted in the denominators. Missing baseline or post baseline results will be excluded from the summary.

3.3.4 Incremental effects of volanesorsen on lipid measures

The incremental effects of volanesorsen on fasting TG and other fasting lipid measurements will be explored and the association between percent changes in fasting lipid measurements and total amount of drug received will be examined. Scatter plots of percent change from baseline in fasting lipid measurements including TG, non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, LDL-C, total cholesterol, and total apoC-III versus total amount of volanesorsen received and corresponding Pearson's correlation coefficient will be presented. For patients treated with volanesorsen in index studies, the **Index Study Baseline** will be used, and for patients treated with placebo in index studies and Group 3 patients, the **Open-label Study Baseline** will be used. The total amount of doses will be the total number of injections (volanesorsen) received from both index studies and open-label study regardless if full dosing is administered or not.

All patients will be presented in the same graph no matter if the patient is from the index studies or the open-label study.

3.3.5 Frequency and severity of patient reported abdominal pain

The maximum intensity of abdominal pain related to disease will be collected on the FCS symptom questionnaire and reported by patients weekly on Bracket electronic patient reported outcomes (ePRO). The average maximum intensity of patient reported abdominal pain score during the on-treatment period will be summarized. The patients' reported results will be mapped to each visit week based on the visit window specified in section 3.2.1. If patients have multiple results within a visit window, the worst score will be used for summary and analysis. The results at Week 1 will not be included in the on-treatment period, since the results are reported retrospectively to collect the symptoms of patients during the past week. The missing data will be imputed by using Next Observation Carried Back (NOCB) if there is a subsequent score available. Otherwise, the missing data after the last available score of each patient will not be imputed.

Two (2) types of summary tables will be provided in the subset of FAS patients who reported any abdominal pain (pain score > 0) during the screening period and Week 1. Baselines are defined in the section 3.2.3.

1. Change from both **Index Study Baseline** and **Open-label Study Baseline** in the average of maximum intensity of patient reported abdominal pain will be summarized.
2. Change from both **Index Study Baseline** and **Open-label Study Baseline** in the worst weekly patient reported maximum intensity abdominal pain score during the treatment period will be summarized.
3. The same method described above will be used to impute the missing data in exploratory analyses.

The abdominal pain score in each week will be categorized to no pain (pain score: 0), mild (pain score: 1–3), moderate (pain score: 4–6), or severe (pain score: 7–10). A summary by the category will also be provided for safety set overall, and for CS6 subjects who roll-over to CS7. Other information of the abdominal pain questionnaires will be listed in a patient data listing.

Summary table and figure for abdominal pain intensity change for patients with pain at baseline in CS6 subjects who roll-over to CS7 will be generated.

3.3.6 Percent change and change from baseline in other fasting lipid measurements

Percent change and absolute change from the **Open-label Study Baseline** at Month 3, Month 6, and Month 12 in this open label study, and percent change and absolute change from the **Index Study Baseline** in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C at index study Month 3, Month 6, and Month, and the open label study Month 3, Month 6, and Month 12 will be summarized. For patients enrolled to extended treatment period, percent change and absolute change from the **Open-label Study Baseline** and percent change and absolute change from the **Index Study Baseline** in fasting TG at Week 64, 76, 90, and 104 will also be summarized. A descriptive summary of these measurements over time will also be conducted overall and by age group (<65 years vs. >=65 years).

3.3.7 Percent change and change from baseline in fasting total apoC-III

Percent change and absolute change from the **Open-label Study Baseline** at Month 3, Month 6, and Month 12 in this open label study and percent change and absolute change from the **Index Study Baseline** in fasting total apoC-III at index study Month 3, Month 6, and Month, and the open label study Month 3, Month 6, and Month 12 will be summarized. For patients enrolled to extended treatment period, percent change and absolute change from the **Open-label Study Baseline** and percent change and absolute change from the **Index Study Baseline** in fasting TG at Week 64, 76, 90, and 104 will also be summarized. A descriptive summary of fasting total apoC-III over time will also be conducted.

3.3.8 Change from baseline in Quality of Life (QOL) questionnaires (EQ-5D, SF-36)

QOL Questionnaires (EQ-5D and SF-36) will be completed by patients at Baseline, Week 13, Week 26 and Week 52 and Week 65.

A shift table for EQ-5D QOL Questionnaire will be provided with the shift from the **Index Study Baseline** level and from the **Open-label Study Baseline** level for each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) to post-baseline visit level. In the shift table, slight and moderate will be combined as one level, and severe and unable will be combined as one level. The health status visual acuity score (VAS), as well as the scores for all dimensions, will be summarized for baseline, post-baseline visit, and the change from baseline at post-baseline visit will be summarized also.

The results of the mean weighted scores for all sections from the SF-36 QOL Questionnaire (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) will be summarized for baseline, post-baseline visit, and the change from baseline at post-baseline visit will be summarized also. Both the **Index Study Baseline** and the **Open-label Study Baseline** will be used.

Note: Group 2 patients have no QOL assessment in the index study (ISIS 304801-CS16).

3.3.9 Adjudicated acute pancreatitis events Rate

Yearly rate of adjudicated acute pancreatitis events and patient reported moderate or severe abdominal pain (pain score: 4-10) for FAS during the on-treatment period of the Open-label study, calculated as 365.25 x the number of events during the on-treatment period / on-treatment duration, will be summarized with descriptive statistics. At each mapped visit window of abdominal pain, at most one moderate or severe event will be counted to calculate the yearly rate. Adjudicated acute pancreatitis event rate prior to first dose of Study Drug (including events based on medical chart review) vs. treatment emergent events will be summarized.

Yearly rate of adjudicated acute pancreatitis events and patient reported moderate or severe abdominal pain (pain score: 4-10) for patients who administered volanesorsen in Index studies will be calculated and summarized, including events occurred during either index study or open-label study.

On-study and on-treatment pancreatitis incidence rate per patient year of exposure will be summarized.

3.3.10 Frequency of other symptoms: eruptive xanthoma, lipemia retinalis

Percentage of patients who experienced eruptive xanthoma during the treatment period of the Open-label study will be summarized. Counts and percentages of the worst severity of eruptive xanthoma will be provided. Yearly rate during the treatment period of the Open-label study, calculated as 365.25 x the number of events during the treatment period / treatment duration, will be summarized with descriptive statistics.

Yearly rate of eruptive xanthoma for patients who administered volanesorsen in the Index study CS6 will be calculated and summarized, including events occurred during either index study or open-label study.

Counts and percentages of lipemia retinalis will be summarized by visits.

3.4 Pharmacokinetic and Immunogenicity Analysis

PK concentration and Immunogenicity (IM) results obtained in the open-label study will be summarized along with those from the index study. Patient data listings will also be provided.

3.4.1 Pharmacokinetic Analysis

PK analyses will be conducted in PK population.

3.4.1.1 All patients

During the treatment period, blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65*
Study Day	D1	D22	D50	D85	D176	D260	D358	D449
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (Extended Treatment Period)

Week	Wk 76	Wk 104	Wk 117
Study Day	D526	D722	D813
Visit Window	2	2	7

+/- Days			
Time Point	Pre-dose	Pre-dose	Anytime

For all patients, 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 Group 1 and Group 2 patients by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and newly enrolled patients as a separate group (Group 3), dose, patient ID, patient immunogenicity (IM) status, and IM onset (if applicable) as defined in Section 3.4.2, and day. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "0.00". In addition, percent differences between scheduled and actual sampling times will also be listed.

For all patients, trough (pre-dose) and post-treatment volanesorsen plasma concentrations will be summarized by the group presented in Section 3.2.1, study day, with and without stratification by IM status, 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 and without stratification by immunogenicity status will be generated.

3.4.1.2 PK subgroup

A subgroup of patients will participate in an extended PK collection. The detailed PK sampling schedules are outlined below. Patients continuing to receive volanesorsen beyond Week 52 will follow the PK sampling schedule in the extended treatment period:

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65**
Study Day	D1	D2	D22	D50	D85	D176	D260	D358	D449
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

** Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and Group 2 Patient). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24h}$ /F) will be calculated from $CL_{0\text{-}24h}$ /F = Actual Dose/$AUC_{0\text{-}24h}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24h} = AUMC_{0\text{-}24h} / AUC_{0\text{-}24h}$, where $AUMC_{0\text{-}24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics for 2 groups (Treatment naive group and CS6-Volanesorsen and CS16-Volanesorsen Combined), with and without stratification by IM status.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately. This SAP do not include relevant analysis plan.

3.4.2 Immunogenicity (IM) Analysis

Immunogenicity (IM) analyses will be conducted in Safety Set.

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

Sample IM status (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen or placebo) will be listed for Group 1 and Group 2 patients by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and newly enrolled patients as a separate group (Group 3) by study day. Subject IM status (positive/negative or unknown) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}) and max and/or end of treatment titer will be listed by treatment and dose.

Additionally, the sample and patient IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated patients with antibody negative, positive, and unknown status by the group presented in Section 3.2.1. Furthermore, onset, and peak titer of the ADA response, if applicable, will be summarized as median, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum).

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and pharmacokinetic measures will be evaluated in an exploratory manner.

3.5 Safety Analyses

Safety endpoints including treatment exposure, AEs, clinical safety lab, vital signs, physical examination, 12-lead ECG, Echocardiogram, prior and concomitant medication use, and MRIs will be summarized in Safety Set.

On-Study period (from **Day 1 of Volanesorsen** to end of the study) in the open-label study will be classified to 3 periods:

- On-treatment period: from the first dose of Volanesorsen to the last dose of Volanesorsen + 28 days
- After-treatment period: from the last dose of Study Drug + 29 days to the last dose of study medication + 90 days
- Post-follow up period: after the last dose of Study Drug + 90 days

For vital sign, clinical safety lab, or 12-lead ECG,

- Visits of summary tables include baseline and labeled post baseline visits in the open-label study.
- **Safety Baseline** is defined in the section 3.2.3 of this SAP.

For AEs, prior and concomitant medication use, each summary table will present the open-label study data.

For treatment exposure, details are discussed in the section 3.5.5 of this SAP.

By patient data listings will display data collected in the open-label study.

In this section, **Day 1 of Volanesorsen** is defined as the first day volanesorsen is administered to the patient. For patients on active treatment in the index study, Day 1 of Volanesorsen will be the first day volanesorsen is administered in the index study. For patients on placebo in the index study, Day 1 of Volanesorsen will be the first day volanesorsen is administered in this open-label study.

Patient profile figures will be generated for selected patients to provide graphical profile of endpoint of interest.

3.5.1 Imputation of Missing/Partial Dates

3.5.1.1 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 **Day 1 of Volanesorsen.**
- If month and day are missing and year is
    - The same as the year of **Day 1 of Volanesorsen** then assign the month-day of first Study Drug.
    - Earlier than the year of **Day 1 of Volanesorsen** then assign December 31.
    - After the year of **Day 1 of Volanesorsen** then assign January 1.

If only day is missing and month-year is

- The same as the month-year of **Day 1 of Volanesorsen** then assign the day of first Study Drug.
- Earlier than the month-year of **Day 1 of Volanesorsen** then assign the last day of the month.
- After the month-year of **Day 1 of Volanesorsen** 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.

3.5.1.2 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 **Day 1 of Volanesorsen**.
- If month and day are missing and year is
    - Earlier than the year of **Day 1 of Volanesorsen** then assign December 31.

- Otherwise, assign January 1.

- If only day is missing and month-year is
  - Earlier than the month-year of **Day 1 of Volanesorsen** 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.

3.5.2 Adverse Events

3.5.2.1 General Analysis of AEs

All adverse events will be coded by the MedDRA coding system. Missing or partial dates will be imputed as outlined in section 3.5.1.1. A treatment emergent adverse event (TEAE) is defined as any event starting or getting worse on or after **Day 1 of Volanesorsen**

In the situation where change in severity (but no change in seriousness) occurs for an adverse event, study sites are instructed to enter an end date and start a new record for the adverse event. In the new record, the changed severity is to be recorded and the start date will be set to be the end date of the previous record. Data linking those records are collected in the data set “Formlinks”.

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 on **Day 1 of Volanesorsen**, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the patient’s first dosing date/time on **Day 1 of Volanesorsen**, then the AE is not treatment-emergent.

Case 2: If there is a “Formlink” link between two AE records, then the two 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 on **Day 1 of Volanesorsen**, 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 second record is changed to serious, 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) and the serious result is not changed from non-serious to serious, then neither record is counted as treatment-emergent.

Case 2b: Both AE records in the pair occur on/after first dosing on **Day 1 of Volanesorsen**.

If the AE severity on the second record is worse than the severity on the first record or the second record is changed to serious, then count both records as treatment-emergent. But, if the severity doesn't worsen and the serious result is not changed from non-serious to serious, then only count the first record as treatment-emergent.

Case 2c: Both AE records in the pair occur before first dosing on **Day 1 of Volanesorsen**.

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.

TEAE will be classified into three periods: on-treatment, after-treatment, and post-follow up periods and are defined as follows based on (imputed) start date of the event.

The frequency of patients with any incidence of AEs and the number of events will be summarized by MedDRA preferred term and system organ class for:

1. Any TEAE, any on-treatment TEAE, any after-treatment TEAE.
2. TEAEs related to Study Drug. Related is defined as "Related", "Possible", or missing relationship to Study Drug.
3. 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.
4. TEAEs potentially related to Study Drug by severity.
5. Post-follow up adverse events
6. Serious TEAEs.
7. Serious on-treatment TEAE.
8. Serious TEAEs potentially related to Study Drug.
9. AEs leading to permanent treatment discontinuation, and
10. TEAEs leading to death.

Adverse event summaries will be presented alphabetically and by descending frequency of the percentage of patients in the overall column. An overview of AEs will be provided for all TEAEs, on-treatment TEAEs, and after-treatment AEs. Treatment-emergent AEs, treatment emergent SAEs, AEs 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 on-treatment, after-treatment, and post-follow up periods. Originally reported dates will be used for listings.

On-study AEs will be also summarized by treatment and age for FCS patients and all patients in safety set.

Treatment emergent renal adverse events will be summarized.

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

3.5.2.2 Adverse Events of Special Interest

The following events are considered to be clinically-relevant and will be summarized:

- Platelet count reduction to< 50,000/mm^3 associated with major bleeding or clinically-relevant non-major bleeding
- Platelet count reduction to < 25,000/mm^3, irrespective of bleeding status

3.5.2.3 Other Events of Interest

Local Cutaneous Reactions at the Injection Site (LCRIS)

Local cutaneous reactions at injection site (LCRIS) will also be summarized by the group presented in Section 3.2.1 including overall using the MedDRA coding system, by system organ class and preferred term. Number and percent of patients reporting at least one LCRIS will be summarized also.

The following MedDRA preferred terms are determined by the Sponsor's Pharmacovigilance personnel to represent the local cutaneous reaction at the injection site:

- Injection site erythema
- Injection site swelling
- Injection site pruritus
- Injection site pain
- Injection site tenderness

Only events that start on the day of injection and persist for at least 2 days, i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after the injection, will be included. Events with onset date on the day of injection and missing resolution date will also be included.

Percentage of injections leading to local cutaneous reactions at injection site will be summarized by the group presented in Section 3.2.1 including overall using descriptive statistics.

Percentage of injections leading to local cutaneous reactions at the injection site will be calculated as follows for each patient: (A/B)*100, where A=number of injections leading to local cutaneous reactions at the injection site, and B=total number of injections.

Revised LCRIS is defined as any AE with MedDRA preferred term or verbatim that contains "INJECTION SITE". Revised LCRIS that start on the day of injection and persist for at least 2 days, and revised LCRIS that start any time and persist for at least 2 days, will be included.

Number of total volanesorsen injections in index study and/or open-label study before the first treatment emergent revised LCRIS will be summarized.

Duration to resolution in days will be calculated as the summation of (AE end date – AE start date) + 1 for all treatment emergent LCRIS related to one injection. For LCRIS events with overlapped duration related to one injection, the earliest start date and latest end date will be used in the calculation; for unresolved LCRIS events with missing end date, the last date on study will be used in the calculation.

Discoloration

Discoloration is defined as any AE with "Injection Site Discolouration" as MedDRA preferred term. Counts and percentages of patients with any discoloration TEAE and unresolved discoloration TEAE will be summarized.

Flu-Like Reactions

Flu-like reactions (FLRs) will also be summarized by the group presented in Section 3.2.1 including overall using the MedDRA coding system, by system organ class and preferred term and by preferred term only. Number and percent of patients reporting at least one FLR will be summarized also.

FLRs are defined as either (A) flu-like illness or (B) Pyrexia or feeling hot or body temperature increased, plus at least two of the following: Chills, Myalgia, and Arthralgia, starting on day of injection or the next day.

Percentage of injections leading to FLRs will be summarized by the group presented in Section 3.2.1 including overall using descriptive statistics.

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

Revised FLRs are defined as flu-like illness, chills, myalgia, arthralgia, pyrexia, feeling hot, body temperature increased that starts on the day of volanesorsen injection or the next day.

Bleeding Adverse Events

Treatment Emergent bleeding adverse events also will be summarized using MedDRA preferred term and system organ class. The bleeding TEAE will be defined based on the Haemorrhages (SMQ) Export from MedDRA.

The frequency of patients with any incidence of AEs and the number of events will be summarized by MedDRA preferred term (and severity) sorted by frequency for:

1. Any treatment emergent bleeding AEs for the safety set, for the subset of patients on concomitant anti-coagulant or anti-platelet medication, and for the subset of patients not on concomitant anti-coagulant or anti-platelet medication.

2. Treatment emergent bleeding AEs under contemporaneous use of concomitant anti-coagulant or anti-platelet medication for the subset of patients on concomitant anti-coagulant or anti-platelet medication.

Treatment emergent bleeding adverse events will be listed. In addition, treatment emergent bleeding adverse events will be listed by platelet count categories before and after bleeding, and anti-platelet or anti-coagulant medication.

Platelet Count Decreased/Thrombocytopenia Events

Platelet count decreased or thrombocytopenia events will be listed by preferred terms, severity, platelet count category, platelet count before (or on)/after AE, and CTCAE grade of platelet count before (or on)/after AE.

List of nadir post-baseline platelet count will be generated for patients who discontinued due to platelet count decreased or thrombocytopenia events.

Any 2 Occurrences of Platelet Count < 140,000/mm^3 or Any Single Occurrence of Platelet Count <100,000/mm^3

The analysis is defined in section 3.5.4.2.

ALT > 3 ULN

The analysis is defined in section 3.5.4.2.

3.5.3 Vital Signs Measurements

Vital signs will include weight, BMI, body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure. Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum) for vital sign values as well as the change from baseline at each study visit.

3.5.4 Laboratory Measurements

3.5.4.1 General analysis of safety laboratory data

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, Glucose, Blood Urea Nitrogen (BUN), Creatinine, Uric Acid, Total bilirubin, Direct (conjugated) bilirubin, Indirect (unconjugated) bilirubin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and 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)
- Other assessments: hs-CRP, C5a, Bb, Sedimentation rate, De-lipidated free glycerol, Glycated Hemoglobin (HbA1c), FPG
- 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 data 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 neutrophils 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.

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

GFR (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).

All lab data will also be displayed in patient data listings based for all enrolled patients. Chemistry, hematology, coagulation, other assessments and quantitative Urinalysis (result, change from safety baseline) will be summarized using descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum) by study visit. Counts and percentages of categorical lab results, e.g. Urine protein will be provided.

3.5.4.2 Additional analyses of key safety laboratory data

The following analyses of key safety laboratory data will be summarized for on-treatment period and on-study period respectively.

The number and percent of patients falling in each of the following categories will be tabulated:

- The higher of ALT > 3 x upper limit of normal (ULN) or ALT > 2 x Safety 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, and
- ALP > 2 x ULN and (safety baseline ALP < 2 x ULN or safety 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 (A confirmed value is based on a consecutive lab value within 7 days. If that value is in the same or worse category 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 at least 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 categorized by value range based on Guidance for Industry – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007), and the incidence of shift from safety baseline to worst post-baseline value taken after the first dose during on-treatment period will be summarized. If a patient is missing a safety 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 safety baseline to worst post-baseline values based on the confirmed results by toxicity grade for ALT, AST, and platelets will also be tabulated.

- Hemoglobin: shift from safety baseline to minimum post-baseline value
- WBCs: shift from safety baseline to minimum post-baseline value
- WBCs: shift from safety baseline to maximum post-baseline value
- Platelets: shift from safety baseline to minimum post-baseline value
- Creatinine: shift from safety baseline to maximum post-baseline value
- BUN: shift from safety baseline to maximum post-baseline value
- ALT: shift from safety baseline to maximum post-baseline value
- AST: shift from safety baseline to maximum post-baseline value

Hemoglobin change from baseline to minimum post-baseline value will be summarized by value category based on the toxicity grade as well.

Selected coagulation assessments shift from baseline to the worst post-baseline value will also be summarized by value category based on the toxicity grade.

- Activated Partial Thromboplastin Time: shift from safety baseline to maximum post-baseline value
- Prothrombin Time: shift from safety baseline to maximum post-baseline value
- Prothrombin Intl. Normalized Ratio: shift from safety baseline to maximum post-baseline value
- Fibrinogen: shift from safety baseline to minimum post-baseline value
- Fibrinogen: shift from safety baseline to maximum post-baseline value

LDL-C will be classified to ≥160 mg/dL (4.14 mmol/L) or <160 mg/dL (4.14 mmol/L), and the incidence rate of shift from safety baseline to maximum post-baseline category will be summarized.

hsCRP will be classified to Normal or > Upper limit of normal (ULN), and the incidence rate of shift from safety baseline to maximum post-baseline category will be summarized.

The incidence of patients with post-baseline platelet results falling in each of the following categories will be summarized for the safety set and the subset of patients with normal baseline ($\geq$140,000/mm^3), and these categories will be summarized based on confirmed values as well:

- 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 or any single occurrence of platelet count <100,000/mm^3
- Worst post-baseline value falling in: 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
- Worst post-baseline platelet reduction from Baseline ≥ 30% and ≥ 50%

The incidence of patients with post-baseline platelet results falling in each of the following categories will be summarized for the safety set and the subset of patients with normal baseline ($\geq$140,000/mm^3):

- With >= 2 consecutive values of platelet count < 140,000/mm^3
- With platelet count <100,000/mm^3 at final visit
- With >= 2 consecutive values of platelet count < 140,000/mm^3 or with platelet count <100,000/mm^3 at final visit

The number of patients with any single occurrence of platelet results at any time, and during post-baseline period, falling in each of the following categories will be summarized for the safety set. These categories will be summarized based on nadir platelet values as well:

- < 140,000/mm^3
- <100,000/mm^3
- 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
- < 25,000/mm^3

The ratio of post-baseline central lab platelet test numbers to total number of injections in open-label study will be summarized. The ratio of post-baseline central and local platelet tests numbers to total number of injections in open-label study will be also summarized.

The time to recover from confirmed platelet values <100,000/mm3 during on-study period will be calculated and summarized by all patients, and patients who complete week 52 (or week 104) with or without any dose pause/dose adjustment.

Summary figures will be generated for platelet counts over time (absolute values, absolute change from baseline, and percent change from baseline) in patients treated with placebo in ISIS 304801-CS6 who then treated with Volanesorsen in ISIS 304801-CS7.

A summary figure will be generated for platelet counts over time (mean and SEM of absolute values) for treatment naïve patients. The first event of platelet count < 50,000/mm^3 will be annotated in the figure. This figure will also be generated by weight group (<70kg; >=70kg).

A scatter plot will be generated for nadir platelet counts during on-treatment period vs. selected factors:

Body Weight (kg)
BMI
The Total Number of Injections
Baseline Spleen Volume (mL)
Baseline Fasting Triglycerides (mmol/L)
Baseline Fasting Apolipoprotein CIII (g/L)

The incidence of patients with post-baseline lab results falling in each of the following categories will be summarized for the safety set:

- Any serum creatinine >=0.3 mg/dL higher than baseline
- Any serum creatinine >=50% higher than baseline
- Final visit serum creatinine >=0.3 mg/dL higher than baseline
- Final visit serum creatinine >=50% higher than baseline

Summary of selected hematology assessment (white blood cell count, neutrophil, hemoglobin, and hematocrit) over time will be generated. Summary of selected urinalysis assessment (urinary protein, and urinary albumin), and normalized urine albumin and protein to creatinine (urine albumin/creatinine ratio, urine protein/creatinine ratio) over time will be generated. Corresponding summary figures will be generated as well. Urine albumin/creatinine ratio will be calculated as 1000 * urine albumin (mg/dL) / urine creatinine (mg/dL),

Shift tables of on-study urine albumin/creatinine ratio and urine protein/creatinine ratio will be generated with below ranges:

Urine Albumin/creatinine ratio	Urine Protein/creatinine ratio
< 30 mg/g	< 150 mg/g
30 to < 300 mg/g	150 to < 500 mg/g
>= 300 mg/g	500 to < 1000 mg/g
	>= 1000 mg/g

A listing for patients with ALT or AST > 3 x ULN will be generated to present all ALT, AST, Bilirubin, and ALP records from central and local lab.

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.

3.5.5 Exposure

Treatment duration in days, number of injections of Study Drug, compliance to Study Drug, dose adjustment and dose interruption/pauses will be summarized for the safety set.

- Treatment duration in days is defined as the last day on Study Drug minus the first day on Study Drug plus one. This will be derived for both index study period and the open-label study period.
- Number of injections of Study Drug received includes those for which full volume of dose was not given.
- Number of injections of Study Drug received for patients on active treatment in the index study will be the number of injections of Study Drug received from the first dose of the index study. Number of injections of Study Drug received for patients on placebo in the index study will be from the first dose of the open-label study.

Treatment duration in months during index study and open-label study will be summarized for the safety set.

- >=3 month category is defined as treatment duration in days >=85 days
- >=6 month category is defined as treatment duration in days >=176 days
- >=9 month category is defined as treatment duration in days >=267 days
- >=12 month category is defined as treatment duration in days >=358 days
- >=18 month category is defined as treatment duration in days >=541 days
- >=24 month category is defined as treatment duration in days >=723 days

Compliance to Study Drug will be summarized by descriptive statistics.

- Compliance of the open-label study for Group 1, Group 2 and Group 3 will be calculated as follows:

  100 x (number of injections of Study Drug in the open-label study) / (number of injections scheduled during the Open-label Study Treatment Period).

- Compliance of the index study (ISIS 304801-CS6 or ISIS 304801-CS16) and open-label study overall for Group 1 and Group 2 will be calculated as follows:

  100 x (number of injections of Study Drug in the index study (ISIS 304801-CS6 or ISIS 304801-CS16)+ number of injections of Study Drug in the open-label study) / (number of injections scheduled during the treatment period in the index study (ISIS 304801-CS6 or ISIS 304801-CS16)+ number of injections scheduled during the treatment period in the open-label study).

3.5.6 Physical Examination

Adverse changes in physical examinations that are deemed clinically significant by the investigator will be classified as AEs. Physical examination results will be listed.

3.5.7 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, 25th percentile, 75th percentile, minimum, and maximum) of the results, as well as the change from baseline to each study visit, will be presented by the group presented in Section 3.2.1 including 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.

3.5.8 Echocardiogram

Echocardiogram results will be listed in a by patient data listing.

3.5.9 Concomitant Medications

Medications start and stop dates that are recorded on the Prior and Concomitant Medications eCRF 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 3.5.1.2. Prior medications include medications started prior to **Day 1 of Volanesorsen** regardless whether continued while on treatment or not. Concomitant medications include medications that patients exposed to on or after **Day 1 of Volanesorsen**. A prior medication with an imputed stop date that is missing or on or after date of **Day 1 of Volanesorsen** 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

2) Concomitant Medication

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

CM = Concomitant Medication, FDD= Date of **Day 1 of Volanesorsen**, LDD= Date of Last 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 Sep 2016).

Prior and concomitant medications will be summarized separately by ATC class, preferred name, treatment group and overall with counts and percentages for the Safety Set by sorting alphabetically and also by decreasing frequency in the overall column. Concomitant anti-coagulant and anti-platelet medications will also be summarized for the Safety Set by decreasing frequency in the overall column.

Additionally, medication changes during the on-treatment period which include those medications that are started, stopped, or changed dose during the on-treatment period (i.e. from **Day 1 of Volanesorsen** to the last dose of Study Drug + 28 days), will be summarized by ATC class, preferred name, treatment group and overall with counts and percentages for the Safety Set by sorting alphabetically and also by decreasing frequency in the overall column.

Prior and concomitant medications will be displayed in patient data 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.

3.5.10 MRIs

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants. The hepatic volume, splenic volume and hepatic fat will be summarized by the group presented in Section 3.2.1 . Change from baseline at Week 52 will be summarized as well.

Liver and spleen MRIs will also be listed in a by-patient data listing.

4 BIBLIOGRAPHY

- Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007

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