A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)

NCT04568434

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Summary of Clinical Study Results

A Study of Olezarsen Administered to Patients With Familial Chylomicronemia Syndrome (FCS) (Balance)

Protocol #: ISIS 678354-CS3
Study dates: November 2020 to October 2023

Thank you to the participants who took part in the study, "A Study of Olezarsen (Formerly Known as AKCEA-APOCIII-L_{Rx}) Administered to Patients With Familial Chylomicronemia Syndrome (FCS)," also known as the Balance study.

This study helped researchers find out if a drug called olezarsen could lower fat particles in blood (triglyceride levels) in participants who live with familial chylomicronemia syndrome (FCS).

Why was this study done?

FCS is a rare genetic disease. Genes are small pieces of DNA that provide instructions to the body to make proteins. Genetic diseases are passed on from parents to children through altered (mutated) genes.

FCS is characterized by the buildup of fat particles (triglycerides) in the blood that can result in severe abdominal pain and other serious health problems. FCS is caused by mutated genes that affect a special protein called lipoprotein lipase (LPL). LPL helps break down triglycerides, which are stored in round particles made of protein and fat called lipoproteins. The body uses lipoproteins to transport fat after consuming food. In people with FCS, LPL is missing or does not work well, and the body is unable to break down triglycerides and process fat. This causes the body to have high levels of lipoproteins containing fats, which means people with FCS must continuously adhere to an extremely strict low-fat diet.

People with FCS have 10 to 100 times the normal amount of triglycerides in their blood. Symptoms of FCS include nausea, vomiting, brain fog, belly pain, and the appearance of small, yellowish bumps on the skin filled with fat. People with FCS are at a high risk of developing a severe condition called pancreatitis, which is the inflammation of the pancreas due to high levels of triglycerides in the blood and can be life-threatening.

The most common treatments for FCS include a very low-fat diet and avoiding any alcohol intake. However, these steps are difficult to achieve for most people. Researchers are looking for medicines that can help lower the triglycerides in the blood and reduce the risk of inflammation of the pancreas.

In this study, researchers looked at a potential new medication called olezarsen. This drug is designed to reduce the actions of a protein called apoC-III, which regulates triglyceride levels in the blood. By lowering levels of apoC-III, researchers expect olezarsen to help lower triglyceride levels. Researchers studied the effects of olezarsen administered to participants with FCS compared with the effects of placebo. A placebo is an inactive substance that looks like and is administered as the study medication but does not actually contain any medicine.

Researchers wanted to learn more about the effect of olezarsen on triglyceride levels and what side effects it may cause. Researchers also wanted to learn if treatment with olezarsen reduced the occurrence of pancreatitis events.

When was this study done?

This study started in November 2020 and ended in October 2023.

Who took part in this study?

Participants could take part if:

- At least 18 years old
- Had FCS
- During screening (determining eligibility), had a triglyceride level of at least 880 milligrams per deciliter (mg/dL) after fasting (not eating). A milligram is one-thousandth of a gram. A gram is about 1/30 of an ounce. A deciliter measure fluid volume that is 1/10 liter. A liter is a little bigger than a quart.

Participants could not take part if they:

- Had acute coronary syndrome, or conditions that reduced or stopped blood flow to the heart, within 6 months of starting the study
- Had major surgery within 3 months of starting the study
- Had other conditions that the researchers believed would interfere with the study

For more information on who could take part in this study, please refer to the websites listed at the end of this summary.

How many people took part in this study?

Altogether, 66 participants took part in this study, of whom 28 were men (42%) and 38 were women (58%). Participants were between 18 and 78 years of age.

The study took place at 29 clinics in Canada, France, Italy, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, the United Kingdom, and the United States.

- 29 participants (44%) enrolled in North America
- 37 participants (56%) enrolled in Europe

What happened during the study?

What did researchers want to know?

Researchers wanted to know how well olezarsen worked to lower triglyceride levels in the blood of participants with FCS.

The main question researchers wanted to answer was:

How did triglyceride levels change after 6 months of treatment in participants who took olezarsen compared with those who took placebo?

To address this question, researchers took blood samples and compared triglyceride levels at the start of the study to triglyceride levels after 6 months of treatment with olezarsen.

Participants had to fast for at least 10 hours before each blood sample was taken.

What treatments were studied?

- Olezarsen, 50 or 80 milligrams (mg), given as an injection under the skin (subcutaneous).
- Placebo, given as an injection under the skin. Both olezarsen and placebo were injected once every 4 weeks.

How was the study done?

There are many types of clinical studies. This study was:

- Phase 3: This is usually the last phase of clinical study before a new drug is submitted to government authorities for approval. A study at this phase is used to confirm the effect of a drug and learn more about how safe and tolerable it is.
- Randomized: Who got which dose of olezarsen or placebo was decided randomly by a computer program.
- Placebo-controlled: Researchers used a placebo to learn the effect of olezarsen.
- Double-Blind: Neither researchers nor participants knew who was getting olezarsen or placebo.

Before the study began, all participants were screened (evaluated) to be sure they were a good fit for the study.

Screening Period

- During the screening, participants were placed on a stable low-fat diet during the first 2 weeks. This diet would continue through the rest of the study.
- The screening included laboratory tests, physical tests, and genetic tests for FCS. The participants were also asked to answer a set of questions (questionnaires) to check their disease state and quality of life.
- The screening lasted for 4 to 8 weeks.

Treatment Period

- Following the screening period, participants were placed into 1 of 2 groups.
- Group 1 received either 50 mg olezarsen or a matching placebo once every 4 weeks. Group 2 received 80 mg olezarsen or a matching placebo also once every 4 weeks.
    - Group 1 had 22 participants receiving olezarsen 80 mg
    - Group 2 had 21 participants receiving olezarsen 50 mg
    - Groups 1 and 2 had a total of 23 participant receiving placebo
- During the treatment, blood samples were collected every 4 weeks to check for the levels of triglycerides in the blood.
- Participants also completed questionnaires to check their own state and symptoms of the disease. They recorded any medical problems they had during the treatment.
- The treatment period lasted for 52 weeks (1 year).

Follow-up Period

- After ending their treatment, participants entered a 13-week follow-up period or an extension study if they completed the entire year of treatment.
- The extension study allowed researchers to collect more information on the safety and effectiveness of olezarsen.
- Those participants who did not move onto the extension study were followed up every 4 weeks of the 13-week follow-up period to check the safety and effectiveness of olezarsen.

Participants had check-up visits at the study clinic, both during treatment and for up to 13 weeks after treatment. Researchers observed participants' health and checked for any side effects.

What were the results of the study?

The results below include all 66 participants who received at least 1 dose of olezarsen or placebo.

How did the triglyceride levels change after 6 months of treatment in participants who took olezarsen compared to those who took placebo?

Researchers wanted to compare the change in fasted triglyceride levels from the start of the study between the olezarsen and placebo groups.

After 6 months:

- The triglyceride levels in the participants who received 80 mg of olezarsen decreased by 44% compared with placebo.
- The triglyceride levels in the participants who received 50 mg of olezarsen decreased by 22% compared with placebo.

Researchers considered the change in the participants who received 80 mg of olezarsen to be meaningful. Results in the group of participants that received 80 mg of olezarsen every 4 weeks had a reduction in triglyceride levels that were statistically significant from placebo. Statistical significance means that the numbers are reliably different, greatly aiding in data analysis. The participants who received 50 mg of olezarsen every 4 weeks had a reduction in triglyceride levels, but compared with placebo, was not statistically significant.

How did the occurrence of pancreatitis change after 1 year of treatment in participants who took olezarsen compared to those who took placebo?

Researchers wanted to compare the occrence of pancreatitis from the start of the study between the olezarsen and placebo groups.

After 1 year there was an 88% decrease in occurence of pancreatitis in participants that received olezarsen compared with placebo. Researchers considered this change to be meaningful.

For more information on the study results, refer to the websites listed at the end of this summary.

What drug-related side effects did participants have during the study?

A summary of the drug-related side effects that happened during the study is shown below. Not all participants had side effects. The results include all participants who received at least 1 dose of olezarsen or placebo.

Side effects are unwanted medical problems thought to be caused by a medicine or a medical treatment.

A side effect is called serious when it results in death, is life-threatening, causes lasting problems, or requires hospital care.

- Total participants: 66
- 13 out of 43 participants (30%) who received olezarsen had side effects.
    - Olezarsen 50 mg group: 6 out of 21 participants (29%) had side effects
    - Olezarsen 80 mg group: 7 out of 22 participants (32%) had side effects
- 5 out of 23 participants (22%) who received placebo had side effects
- No participants in any group had serious side effects.
- 2 out of 43 participants (5%) who received olezarsen stopped treatment due to side effects.
    - Olezarsen 50 mg group: 0 participants stopped treatment
    - Olezarsen 80 mg group: 2 out of 22 participants (9%) stopped treatment
    - Placebo group: 0 participants stopped treatment
- No participants died due to side effects.

The most common side effects that were reported in at least 15% of participants were:

- Corona Virus (COVID19)
  - 6 out of 21 participants (29%) who received olezarsen 50 mg
  - 3 out of 22 participants (14%) who received olezarsen 80 mg
  - 8 out of 23 participants (35%) who received placebo
- Abdominal Pain
  - 3 out of 21 participants (14%) who received olezarsen 50 mg
  - 4 out of 22 participants (18%) who received olezarsen 80 mg
  - 8 out of 23 participants (35%) who received placebo
- Diarrhea
  - 1 out of 21 participants (5%) who received olezarsen 50 mg
  - 2 out of 22 participants (9%) who received olezarsen 80 mg
  - 6 out of 23 participants (26%) who received placebo
- Headache
  - 4 out of 21 participants (19%) who received olezarsen 50 mg
  - 1 out of 22 participants (5%) who received olezarsen 80 mg
  - 3 out of 23 participants (13%) who received placebo
- Pancreatitis
  - 2 out of 21 participants (10%) who received olezarsen 50 mg
  - 1 out of 22 participants (5%) who received olezarsen 80 mg
  - 4 out of 23 participants (17%) who received placebo
- Fatigue
  - 1 out of 21 participants (5%) who received olezarsen 50 mg
  - 1 out of 22 participants (5%) who received olezarsen 80 mg
  - 4 out of 23 participants (17%) who received placebo

How has this study helped patients and researchers?

Researchers look at the results of many studies to decide which medicines work and are safest for participants. This summary gives the results of 66 participants in a single study. Other studies may have more participants and may give different results.

Overall, researchers learned that olezarsen 80 mg led to a meaningful reduction in the levels of triglycerides in the blood after treatment. Researchers also found no new serious safety concerns with olezarsen.

Findings from this study may be used in other studies to learn more about the use of olezarsen in participants with FCS.

Are there plans for further studies?

Further clinical studies with olezarsen are ongoing at this time.

Where can I find out more about this study?

- Official Title of this Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{Rx} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
- Protocol Number: ISIS 678354-CS3
- EU Study Number: 2020-002536-67

https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-002536-67

- US Study Number: NCT04568434

https://www.clinicaltrials.gov/study/NCT04568434

- New England Journal of Medicine Publication

Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *The New England Journal of Medicine*. 2024.

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ISIS 678354-CS3
(AKCEA-APOCIII-L_{Rx})

Balance
a familial chylomicronemia syndrome study

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment 9 – 2 August 2023

EudraCT No: 2020-002536-67

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ISIS 678354-CS3

Amendment 9

EudraCT No: 2020-002536-67

Clinical Phase: 3

Balance
a familial chylomicronemia syndrome study

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol History:

Original Protocol:	21 May 2020
Amendment 1:	7 August 2020
Amendment 2:	30 October 2020
Amendment 3:	22 December 2020
Amendment 4:	12 March 2021
Amendment 5:	16 April 2021
Amendment 6:	25 October 2021
Amendment 7:	26 October 2022
Amendment 8:	19 June 2023

Sponsor
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See electronic signature and date attached at end of document

[redacted]
[redacted] Clinical Development [redacted]

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc and Akcea Therapeutics, Inc. that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc. and Akcea Therapeutics, Inc.

Protocol Signature Page

Protocol Number:	ISIS 678354-CS3
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 9
Date:	2 August 2023

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)" dated 2 August 2023, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

_____
Investigator's Signature

_____ _____
Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 678354-CS3

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L$_{RX}$ Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment Number: 9

Amendment Date: 2 August 2023

The following table provides a summary list of modifications to Protocol ISIS 678354-CS3 Amendment 8, dated 19 June 2023. Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

Protocol Section	Description of Change	Rationale
Synopsis Section 1.1.2 Section 1.2.2 Section 10.5 Interim Analysis and Multiplicity	• The following secondary points were added: ○ Secondary endpoint: comparison of adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53/ET) between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening ○ Secondary endpoint: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening • The following secondary endpoints were changed as noted with deletions in strike-through and additions in bold: ○ Secondary endpoint: comparison of proportion of patients who achieve fasting TG ≤ ~~750~~**880** mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS ○ Secondary endpoint: comparison of proportion of patients who achieve fasting TG ≤ ~~750~~**880** mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS • The testing sequence for the secondary endpoints was updated	Endpoints were added in line with the stratification criteria of patients with a prior history of pancreatitis within 10 years prior to Screening. Endpoints were changed from achieving fasting TG ≤ 750 mg/dL to achieving fasting TG ≤ 880 mg/dL in line with the inclusion criteria of fasting TG ≥ 880 mg/dL (10 mmol/L) at Screening.

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Primary Objective	To evaluate the efficacy of ISIS 678354 as compared to placebo on the percent change in fasting triglycerides (TG) from Baseline
Secondary Objectives	• Percent change in fasting apoC-III from Baseline • Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline • Percent change in fasting apoB-48 from Baseline • Percent change in fasting non-HDL-C from Baseline • Adjudicated acute pancreatitis event rate in patients with a prior history of pancreatitis within 10 years prior to Screening • Adjudicated acute pancreatitis event rate • Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline • Proportion of patients who achieve fasting TG ≤ 880 mg/dL (10 mmol/L) • Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment • Proportion of patients who achieve fasting TG ≤ 500 mg/dL (5.7 mmol/L)
Additional / Exploratory Objectives	Patient reported abdominal pain, other FCS-related symptoms, diet, and impacts, health-related quality of life (HRQoL), cognitive function, and emergency room (ER) visits, incidence of all-cause hospitalizations and total inpatient days
Safety Objective	To evaluate the safety and tolerability of ISIS 678354
Study Design	This is a multi-center, randomized, double-blind, placebo-controlled study. Eligible patients will enter an approximately 4-week, but no more than 8-week, Screening Period that includes an at least 2-week diet stabilization/run-in period for patients not already on a stable diet, and an approximately 2-week qualification period. Following qualification, approximately 60 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 2:1 to receive ISIS 678354 or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of ISIS 678354 once every 4 weeks or matching volume of placebo (0.5 mL) Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg ISIS 678354 once every 4 weeks or matching volume of placebo (0.8 mL) Weeks 1-49 of the Treatment Period. Randomization will be stratified by (1) prior history of pancreatitis (within 10 years prior to Screening) and (2) previous treatment with volanesorsen. 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. Following the Week 53 visit, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the institutional review board/independent ethics committee (IRB/IEC) and the appropriate regulatory authority.

PROTOCOL SYNOPSIS (CONTINUED)

Study Design (Continued)	Patients not participating in the OLE will enter the 13-week Post-Treatment Evaluation Period. The primary endpoint for the study will be evaluated after the last patient has completed the Week 53/ET Visit and will be based on the percent change in fasting TG from Baseline at the primary analysis time point (Month 6).
Number of Patients	Approximately 60
Study Population	**Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Aged ≥ 18 years at the time of informed consent 3. A diagnosis of Familial Chylomicronemia Syndrome (type 1 Hyperlipoproteinemia) by documentation of confirmed homozygote, compound heterozygote or double heterozygote for loss-of-function mutations in type 1-causing genes (such as *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, *GPD1,* or *LMF1*) 4. Fasting TG ≥ 880 mg/dL (10 mmol/L) at Screening. If the fasting TG is < 880 mg/dL up to 2 additional tests may be performed with any single test used to qualify 5. History of pancreatitis (defined as a recorded diagnosis of acute pancreatitis or hospitalization or emergency room (ER) visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made) within 10 years prior to Screening. Patients without a recorded history of pancreatitis, or no recorded history within 10 years prior to Screening, are also eligible but their enrollment will be capped at 35% (i.e., ≤ 21 of the 60 planned patients) 6. Willing to follow a diet comprising ≤ 20 g fat per day during the study 7. Willing to complete all Patient Reported Outcome assessments throughout the study as described in Section 6.2.5

PROTOCOL SYNOPSIS (CONTINUED)

Study Population (Continued)	**Inclusion Criteria (Continued)** 8. Satisfy the following: a. Females: must be non-pregnant and non-lactating and either: i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) ii. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved) iii. abstinent* or **b.** if engaged in sexual relations of child-bearing potential, agree to use a highly effective contraceptive method from the time of signing the informed consent form until at least 17 weeks after the last dose of Study Drug (ISIS 678354 or placebo)Males: Surgically sterile, abstinent*, or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing a highly effective contraceptive method from the time of signing the informed consent form until at least 17 weeks after the last dose of Study Drug (ISIS 678354 or placebo) * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception 9. Atypical antipsychotic medications (e.g., olanzapine and clozapine) will be allowed if on a stable dose for at least 3 months prior to Screening and dose and regimen expected to remain constant through the end of their participation in this study 10. The following concomitant medications will be allowed if on a stable dose for at least 4 weeks prior to Screening and dose and regimen expected to remain constant through the end of their participation in this study (occasional or intermittent use of over-the-counter (OTC) medications will be allowed at Investigator's discretion): a. Statins, omega-3 fatty acids (prescription and OTC), fibrates, or other lipid-lowering medications. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand through the end of the study b. Antidiabetic medications c. Antihypertensive medications d. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) and regular clinical monitoring is performed e. Tamoxifen, estrogens or progestins

PROTOCOL SYNOPSIS (CONTINUED)

Study Population (Continued)	**Exclusion Criteria** 1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination 2. Active pancreatitis within 4 weeks prior to Screening 3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion: a. Platelet count < 100K/mm^3 at Screening or Qualification. If the platelet count is < 100K/mm^3 up to 2 additional tests may be performed to qualify at both Screening and Qualification b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3.0 × upper limit of normal (ULN) c. Total bilirubin > ULN unless due to Gilbert's syndrome d. Estimated GFR< 45 mL/min/1.73 m^2 [as determined by the CKD-EPI formula for creatinine clearance; (Levey et al. 2009)] e. Urine protein/creatinine ratio (UPCR) ≥ 500 mg/g or urine albumin/creatinine ratio (UACR) ≥ 300 mg/g 4. Uncontrolled arterial hypertension (blood pressure [BP] > 160/100 mmHg) 5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening 6. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 or active Covid-19 infection with or without therapy that will not be resolved by Study Day 1 7. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor 8. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor 9. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 10. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 11. Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening, or 5 half-lives, whichever is longer. This exclusion does not apply to vaccines

PROTOCOL SYNOPSIS (CONTINUED)

Study Population (Continued)	**Exclusion Criteria (Continued)** 12. Concomitant medication/procedure restrictions: a. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening and during the study unless approved by the Sponsor Medical Monitor b. Plasma apheresis within 4 weeks prior to Screening or planned during the study 13. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 14. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study
Treatment Groups	Cohort A (n = 30): Patients will be randomized 2:1 to receive 50 mg ISIS 678354 or matching volume of placebo SC once every 4 weeks for Weeks 1-49. Cohort B (n = 30): Patients will be randomized 2:1 to receive 80 mg ISIS 678354 or matching volume of placebo SC once every 4 weeks for Weeks 1-49.
Study Drug Administration	ISIS 678354 or placebo will be administered as subcutaneous (SC) injections.
Rationale for Dose and Schedule Selection	Doses of 50 mg or 80 mg once every 4 weeks were chosen based on the pre-clinical data and the pharmacodynamic and safety analysis of the Phase 1 study in healthy volunteers with hypertriglyceridemia and the Phase 2 study in patients with hypertriglyceridemia and established cardiovascular disease (CVD) or at high risk for CVD.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • An approximately 4-week, but no more than 8-week, Screening Period • A 53-week Treatment Period during which Study Drug will be administered as a once every-4-week SC injection (Week 1 through Week 49) • A 13-week Post-Treatment Evaluation Period or transition to OLE Study Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, ISIS 678354 plasma trough concentrations, anti-drug antibody (ADA) testing, electrocardiogram (ECGs), and patient reported outcome (PRO) assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will commence at the start of the diet stabilization period and will be repeated at intervals throughout the Treatment and Follow-up Period. Following the Week 53 visit, eligible patients may elect to enroll in the OLE study pending study approval by the IRB/IEC and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post-Treatment Evaluation Period

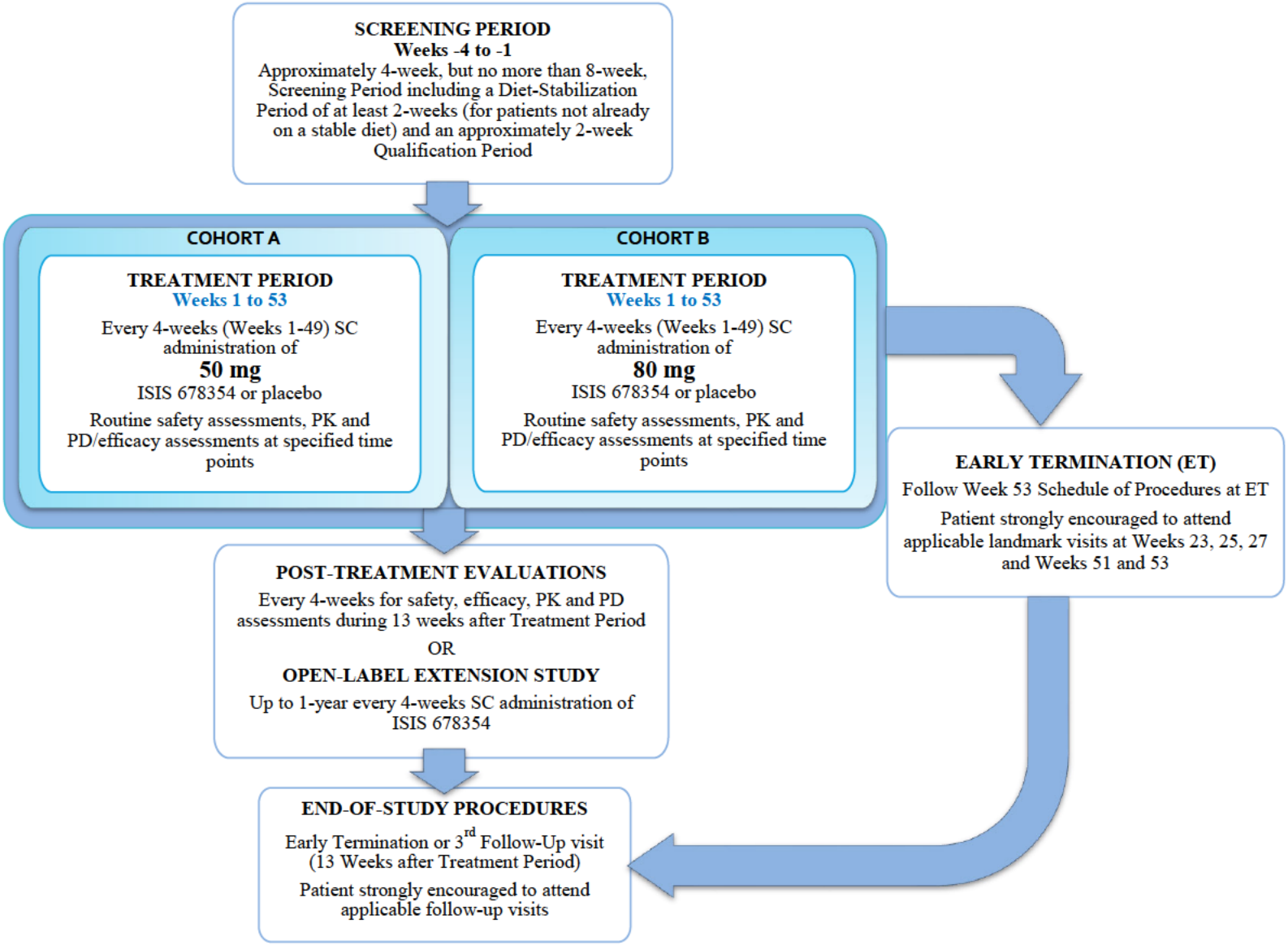
PROTOCOL SYNOPSIS (CONTINUED)

Primary Endpoint	The primary endpoint is the percent change in fasting TG from Baseline at 6 months (average of Weeks 23, 25 and 27) compared to placebo
Secondary Endpoints	Secondary endpoints include the following: • Percent change in fasting TG from Baseline at 12 months (average of Week 51 and Week 53) compared to placebo • Percent change in fasting apoC-III from Baseline at 6 months compared to placebo • Percent change in fasting apoC-III from Baseline at 12 months compared to placebo • Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline at 6 months compared to placebo • Percent change in fasting apoB-48 from Baseline at 6 months compared to placebo • Percent change in fasting non-HDL-C from Baseline at 6 months compared to placebo • Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with a history of pancreatitis within 10 years prior to Screening • Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo • Adjudicated acute pancreatitis event rate from Week 13 through Week 53 compared to placebo in patients with a history of pancreatitis within 10 years prior to Screening • Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo • Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline at 6 months compared to placebo • Percent change in fasting non-HDL-C from Baseline at 12 months compared to placebo • Percent change in fasting apoB-48 from Baseline at 12 months compared to placebo • Proportion of patients who achieve fasting TG ≤ 880 mg/dL at 6 months compared to placebo • Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment • Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo, in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment • Proportion of patients who achieve fasting TG ≤ 500 mg/dL at 6 months compared to placebo
Additional/ Exploratory Endpoints	Frequency and severity of patient-reported abdominal pain and other FCS-related symptoms, diet, and impacts, HRQoL, cognitive function, and ER visits, incidence of all-cause hospitalizations and total inpatient days, compared to placebo

PROTOCOL SYNOPSIS (CONTINUED)

Safety Endpoints	Safety and tolerability assessments include adverse events, clinical laboratory tests, ECGs, use of concomitant medications, and independently adjudicated events rates of Major Adverse Cardiovascular Events (MACE) for ISIS 678354 as compared to placebo
Statistical Considerations	Sample Size Considerations: Based upon prior clinical trial experience with FCS patients, the standard deviation (SD) of the percent change from Baseline in TGs is approximately 46%. With 14 patients in each ISIS 678354 treatment group and 14 in the pooled placebo group, there would be a 90% power to detect a 60% difference between each ISIS 678354 treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the ISIS 678354 treatment patients and no change in the placebo patients. Approximately 60 patients will be enrolled in this trial to account for potential early dropouts and to facilitate safety evaluations. Eligible patients will be randomized 1:1 to Cohort A or Cohort B and each cohort further randomized 2:1 (ISIS 678354:placebo) and stratified for: • Prior history of pancreatitis within 10 years prior to Screening* vs. no history of pancreatitis or no history within 10 years prior to Screening • Previous treatment with volanesorsen * History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made
Sponsor/Licensee	Ionis Pharmaceuticals, Inc. / Akcea Therapeutics, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
apoB-48	apolipoprotein B-48
apoC-III	apolipoprotein C-III
aPTT	activated partial thromboplastin time
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
BUN	blood urea nitrogen
CAD	coronary artery disease
CIR	copy increment from reference
CL	systemic clearance
C_{max}	maximum concentration
CRP	c-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CVD	cardiovascular disease
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated GFR
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
$GalNAc_3$	triantenary *N*-acetyl galactosamine
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IDL	intermediate density lipoprotein
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IM	immunogenicity
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISIS 678354	antisense inhibitor of apoC-III
LDL	low-density lipoprotein

LLN	lower limit of normal
LMF1	lipase maturation Factor 1
MACE	major adverse cardiovascular event
MAD	multiple-ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
mRNA	messenger ribonucleic acid
NCS	not clinically significant
Non-HDL-C	non-high-density lipoprotein-cholesterol
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
on study	The patient is 'on study' from signing of the informed consent until their last study visit
OTC	over-the-counter
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLT	platelet
PPS	per protocol set
PT	prothrombin time
RDW	red cell distribution width
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
siRNA	small interfering ribonucleic acid
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 678354 or placebo
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TG	triglycerides
TRL	TG-rich lipoproteins
UACR	urine/albumin creatinine ratio
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VLDL	very low-density lipoprotein

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objective

To evaluate the efficacy of ISIS 678354 as compared to placebo on the percent change in fasting triglycerides (TG) from Baseline.

1.1.2. Secondary Objectives

To evaluate the efficacy of ISIS 678354 as compared to placebo on the following:

- Percent change in fasting apoC-III from Baseline
- Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline
- Percent change in fasting apoB-48 from Baseline
- Percent change in fasting non-HDL-C from Baseline
- Adjudicated acute pancreatitis event rate in patients with a prior history of pancreatitis within 10 years prior to Screening
- Adjudicated acute pancreatitis event rate
- Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline
- Proportion of patients who achieve fasting TG ≤ 880 mg/dL (10 mmol/L)
- Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Proportion of patients who achieve fasting TG ≤ 500 mg/dL (5.7 mmol/L)

1.1.3. Additional/Exploratory Objectives

To evaluate the effect of ISIS 678354 as compared to placebo on:

- Patient-reported abdominal pain, other FCS-related symptoms (physical fatigue, difficulty thinking and diarrhea), diet, and impacts, health-related quality of life (HRQoL), and cognitive function (Appendix E)
- Emergency room (ER) visits, incidence of all-cause hospitalizations and total inpatient days

1.2. Study Endpoints

The primary analysis time point is at the end of Month 6 where the value is defined as the average of Weeks 23, 25 and 27 assessments.

1.2.1. Primary Endpoint

The primary endpoint is the percent change in fasting TG from Baseline at 6 months (average of Weeks 23, 25, and 27) compared to placebo.

1.2.2. Secondary Endpoints

The secondary endpoints include the following:

- Percent change in fasting TG from Baseline at 12 months (average of Weeks 51 and 53) compared to placebo
- Percent change in fasting apoC-III from Baseline at 6 months compared to placebo
- Percent change in fasting apoC-III from Baseline at 12 months compared to placebo
- Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline at 6 months compared to placebo
- Percent change in fasting apoB-48 from Baseline at 6 months compared to placebo
- Percent change in fasting non-HDL-C from Baseline at 6 months compared to placebo
- Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with a prior history of pancreatitis within 10 years prior to Screening
- Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo
- Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with a prior history of pancreatitis within 10 years prior to Screening
- Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo
- Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline at 6 months compared to placebo
- Percent change in fasting non-HDL-C from Baseline at 12 months compared to placebo
- Percent change in fasting apoB-48 from Baseline at 12 months compared to placebo
- Proportion of patients who achieve fasting TG ≤ 880 mg/dL at 6 months compared to placebo
- Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Proportion of patients who achieve fasting TG ≤ 500 mg/dL at 6 months compared to placebo

1.2.3. Additional/Exploratory Endpoints

Exploratory endpoints include the following:

- Frequency and severity of patient-reported abdominal pain and other FCS-related symptoms (including physical fatigue, difficulty thinking and diarrhea), diet, and impacts, HRQoL, cognitive function, (Appendix E) and ER visits, incidence of all-cause hospitalizations and total inpatient days, compared to placebo

1.2.4. Safety Endpoints

Safety and tolerability assessments include adverse events, clinical laboratory tests, electrocardiogram (ECGs), use of concomitant medications, and independently adjudicated event rate of MACE for ISIS 678354 as compared to placebo.

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

FCS is characterized by frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and in children, can result in a failure to thrive (Brunzell 1999; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011). Fasting plasma TG levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999).

Patients with FCS often present in infancy or childhood with recurrent episodes of abdominal pain or pancreatitis, eruptive xanthomas or hepatomegaly. The diagnosis of FCS is then established by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post-heparin plasma (Brunzell 1999).

Patients with FCS carry a heavy burden of medical complications, the most serious being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, one hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, resulting in release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

FCS significantly affects patients' HRQoL. Bloating, generalized abdominal pain, asthenia, anxiety about potential painful attacks and overall health, difficulty concentrating and "brain

fog" are commonly reported symptoms of FCS. The psychosocial burden of FCS is also increased by dietary fat restriction and overall interference with social interactions and ability to work (Davidson et al. 2017; Gelrud et al. 2017; Davidson et al. 2018; Fox et al. 2020).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective TG clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze TGs in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting TG clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009), glycosylphosphotidylinositol-anchored HDL-binding protein 1 (GP1HBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2. Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma TG levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Gordts et al. 2016), (Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of TG-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to low-density lipoprotein (LDL) (Mann et al. 1997; Brown et al. 2010; Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of very low-density lipoprotein triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

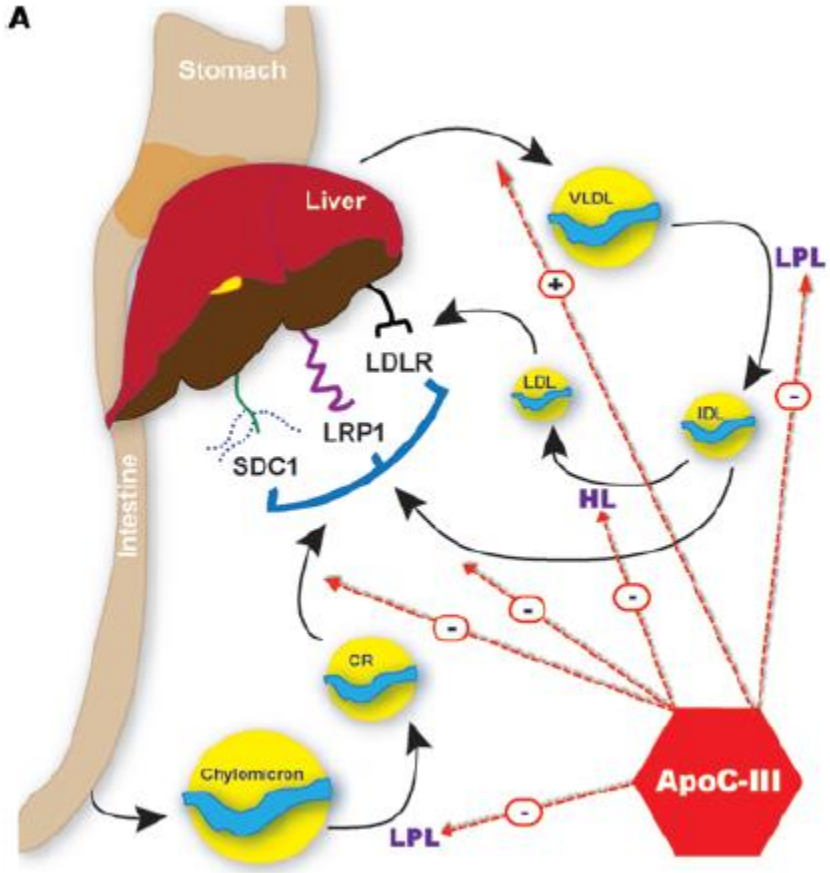


Figure 1: A Schematic Overview of the Possible Effects of ApoC-III on TRL Metabolism

From (Gordts et al. 2016); apoC-III = apolipoprotein CIII, CR = chylomicron remnant, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LDL = low-density lipoprotein, LDLR = LDL receptor, LPL = lipoprotein lipase, LRP1 = low-density lipoprotein receptor related protein 1, SDC1 = syndecan-1, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotype associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the APOC3 gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of

apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating TG and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

The mechanistic data available to date on apoC-III function indicates that lowering apoC-III will produce clinically relevant reductions in TGs as observed with ISIS 678354 treatment in healthy volunteers and in patients with high TGs. In particular, because apoC-III inhibits clearance of TRL in uptake in the liver, a mechanism independent of LPL activity, it will lower TG levels even in patients with FCS who lack any LPL activity. This was clearly demonstrated with the profound reductions in TGs observed with volanesorsen, another antisense inhibitor of apoC-III, in patients who had absent or very low LPL activity (Witztum et al. 2019). Therefore, ISIS 678354 is expected to effectively lower TG levels in FCS patients and may have the potential to reduce events of pancreatitis in this patient population. To this end, volanesorsen was granted approval in the European Union on 3 May 2019.

2.3. ISIS 678354

ISIS 678354 is an antisense oligonucleotide (ASO) inhibitor of apoC-III production. Specifically, ISIS 678354 is a second-generation 2′-*O*-methoxyethyl chimeric ASO covalently bound to triantenary *N*-acetyl galactosamine ($GalNAc_3$), a high affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) (Prakash et al. 2014). The ASO portion of ISIS 678354, volanesorsen, is designed to bind to the human apoC-III messenger ribonucleic acid (mRNA) and has demonstrated robust pharmacology in healthy volunteers and patients, including patients with the most severe form of hypertriglyceridemia, FCS (Graham et al. 2013; Gaudet et al. 2014; 2015). ISIS 678354, having a $GalNAc_3$ conjugate, targets the ASGPR to dramatically increase uptake of the ASO to hepatocytes, thereby decreasing the doses needed to reduce apoC-III over the unconjugated parent molecule, ISIS 304801. ISIS 678354, therefore, has the potential to lower apoC-III and TG with an enhanced tolerability profile over the parent molecule, ISIS 304801.

2.3.1. Mechanism of Action

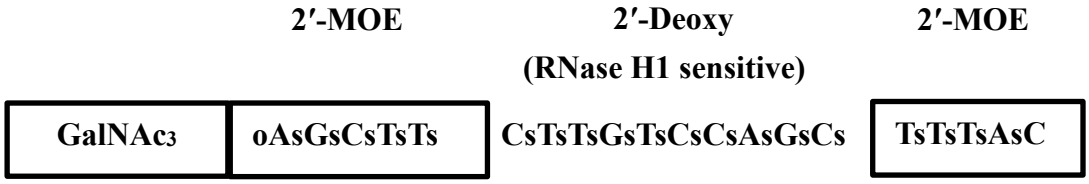
The hybridization (binding) of ISIS 678354 to the cognate mRNA results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Bennett 2007; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2. Chemistry

Chemically, ISIS 678354 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages, with a 5′-trishexylamino-(THA)-C_6GalNAc$_3$ endcap.

The nucleotide sequence of ISIS 678354 (Figure 2) is fully complementary to base-pair positions 489-508 (within the 3′ non-translated sequence of the apoC-III mRNA) and binds to the mRNA by Watson-Crick base pairing. Based on *in silico* analysis, it is not predicted to target any other human gene. Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-gapmer, and ISIS 678354 employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

The fourth region is comprised of a cluster of GalNAc$_3$ sugars which is linked to the 5′-end of ISIS 678354 via a phosphodiester linkage. The GalNAc$_3$ cluster is a high affinity ligand for the ASGPR, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc$_3$ cluster enhances delivery of ISIS 678354 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc$_3$ cluster is metabolized to release ‘free ASO’ inside the cell (Prakash et al. 2014).



$GalNAc_3$ = THA-GalNAc cluster
2′-MOE = 2′-methoxylethyl RNA
2′-Deoxy = DNA
s = phosphorothioate linkage
o = phosphodiester linkage

Figure 2: Design of ISIS 678354, a $GalNAc_3$ Conjugated Chimeric 2′-MOE Phosphorothioate Oligonucleotide

2.3.3. Preclinical Experience

Detailed information concerning the preclinical studies conducted with ISIS 678354 can be found in the Investigator's Brochure.

General toxicology and pharmacokinetic (PK) studies for ISIS 678354 included sub-chronic (13-week repeat-dose studies with a 13-week recovery) and chronic (26-week in mice with a 13-week recovery and 39-week in monkey with a 26-week recovery) toxicity studies. ISIS 838707 (mouse-specific apoC-III inhibitor) was also included in the chronic toxicity study in mice to evaluate any potential toxicity associated with apoC-III inhibition. The following findings in the ISIS 678354 mouse and monkey studies are considered non-specific class effects related to the uptake and accumulation of 2′-MOE ASOs, and the targeted delivery of ASO to the hepatocytes by the $GalNAc_3$ conjugate which results in higher hepatocellular concentrations compared to unconjugated 2′-MOE ASOs. This is most apparent in mice at doses of 20 and 24 mg/kg/wk and in monkey at doses of 12 and 30 mg/kg/wk.

- dose-dependent microscopic findings related to ASO tissue accumulation included the presence of basophilic granules in various tissues in mice and monkeys (liver, kidney, lymph node, bone marrow and skin/injection sites) resulting in adaptive responses such as hypertrophy and/or vacuolation at 30 mg/kg/wk.
- in mice, dose-dependent increases in mitotic figures, cytoplasmic alteration and karyomegaly of hepatocytes and/or infiltration by vacuolated/granular macrophages predominantly at ≥ 6 mg/kg/wk (~50 to ~100 mg/wk human equivalent dose (HED) assuming 70 kg human body weight and 5- to 8-fold scaling factor for mouse plasma PK established for 2′-MOE ASO; (Yu et al. 2015), and mild-to-occasionally marked increases in ALT (~6.5-fold over control) and/or AST (~2.6-fold over control) predominantly at 20 mg/kg/wk (~165 to 350 mg/wk HED). Individual hepatocellular necrosis was observed in one male at 20 mg/kg/wk after 26 weeks of treatment which correlated with an increase in ALT and AST.

- in monkeys, compared to baseline values, increases in glutamate dehydrogenase (GLDH) and ALT (up to ~5- and 4-fold over control, respectively) were observed at ≥ 6 mg/kg/wk (420 mg/wk HED assuming 70 kg human body weight and direct scaling to humans on the basis of body weight) after 39 weeks of treatment with no microscopic correlates.
- pro-inflammatory changes in mice and monkeys after up to 26 and 39 weeks of treatment, respectively, included slight increases in liver weights (up to ~1.6- and up to ~2.1-fold over control) mainly at ≥ 6 and ≥ 12 mg/kg/wk in mice and monkeys, respectively. Increased spleen weights (up to ~1.9- and up to ~2.5-fold over control) were also observed mainly at ≥ 6 and ≥ 12 mg/kg/wk in mice and monkeys, respectively. In mice, increased MCP-1 (up to 7.7-fold over control) was accompanied by splenomegaly and multi-organ vacuolated/granular macrophage infiltrates in the 20 mg/kg/wk dose group.
- in monkeys, sporadic incidences of minimal to marked mononuclear cell infiltration at injection site skin were seen in all dose groups.

The most noteworthy finding in the monkey study was a marked platelet (PLT) reduction, which occurred in 1 male monkey at the mid-high dose level, 12 mg/kg/wk (840 mg/wk HED). At Day 65, this animal presented with petechia and oral mucosal bleeding with a PLT count of $8 \times 10^3/\mu L$. This animal was treated with methylprednisolone on Days 65 and 72, and the PLT count quickly recovered to $145 \times 10^3/\mu L$ on Day 70. This animal continued treatment with ISIS 678354, without a dosing holiday, until scheduled necropsy on Day 93 (interim) with the last clinical pathology evaluation on Day 93 again showing a marked reduction in PLT count ($6 \times 10^3/\mu L$). Marked PLT reductions were not observed in the 30 mg/kg/wk dose group (2100 mg/wk HED) for up to 13 weeks or in any of the remaining dose groups for up to 39 weeks.

In vivo safety pharmacology and *in vitro* genetic toxicity studies indicate that ISIS 678354:

- had no effects on cardiovascular (blood pressure [BP], heart rate [HR], ECG), respiratory (respiration rate, arterial blood gases), or central nervous system (CNS) parameters in the monkey consistent with previous experience with 2′-MOE ASOs (Kim et al. 2014).
- was not genotoxic and did not increase the rate of mutations in the *in vitro* bacterial reverse mutation assay nor induce chromosomal abnormalities in mammalian cells.

2.3.4. Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 678354 can be found in the Investigator's Brochure. A summary of the studies that has been conducted with ISIS 678354 is included below.

ISIS 678354-CS1 was a Phase 1, double-blind, placebo-controlled, dose-escalation study designed to assess the safety, tolerability and PK of single and multiple doses of ISIS 678354 administered by subcutaneous (SC) injection to healthy subjects (age 18 to 65). In the single-ascending dose (SAD) part of the study, 5 dose levels (10, 30, 60, 90, and 120 mg) were evaluated sequentially. In the multiple-ascending dose (MAD) part, 2 dose levels (15 and

30 mg) were evaluated at weekly dosing for 6 weeks and 1 dose level (60 mg) was evaluated at every-4-week dosing for 3 months. The SAD and weekly MAD dose levels were studied in a cohort of 8 subjects, where 6 were randomized to active treatment with ISIS 678354 and 2 were randomized to placebo. In the every-4-week MAD cohort 10 subjects were studied (6 active and 4 placebo). In the 90 and 120 mg SAD and all of the MAD cohorts, the pharmacodynamic effects of ISIS 678354 vs. placebo were examined in healthy subjects with elevated triglycerides (TG > 200 mg/dL).

Results from the SAD portion of the Phase 1 study showed significant dose-dependent sustained reductions in fasting total apoC-III and TG levels. ApoC-III reductions of -4%, -32%, -65%, -78%, and -91%, and TG reductions of -12%, -11%, -43%, -68%, and -77% were observed with single doses of 10, 30, 60, 90 and 120 mg of ISIS 678354, respectively, 14 days after dosing. In the MAD cohorts, mean apoC-III reductions of -65%, -84%, and -83% and mean TG reductions of -61%, -71%, and -65% were observed in the 15 and 30 mg weekly and 60 mg every 4-week dosing cohorts, respectively, 1 week after the last dose. Significant dose-dependent reductions of up to ~ -30% in apoB and increases of up to ~100% in HDL-C were also observed. There were no notable increases in LDL-C in any dose group. Effects were sustained for at least 4 weeks after the last dose, consistent with the drug's long terminal elimination half-life.

Overall, ISIS 678354 was well-tolerated and there were no safety concerns. There were no deaths, no serious AEs (SAE) related to ISIS 678354, no AEs leading to treatment discontinuation, and no clinically significant trends in laboratory assessments observed in any of the ISIS 678354 Phase 1 dose groups. Two (2) of 6 subjects receiving ISIS 678354 every 4 weeks, each experienced ALT increased (1 event in each subject of moderate severity) and single events of AST increased. These events were considered possibly related to Study Drug and were the only events experienced by more than 1 subject receiving ISIS 678354 in the every 4-weeks multiple-dose cohort. Both subjects had prior history of AST and ALT elevations suggesting a medical history that may have contributed to the observed liver enzyme elevations during the study. Also, other dose cohorts with similar cumulative doses, the 120 mg single dose and 30 mg weekly dose, were not associated with increases in AST or ALT. There were no other treatment-related laboratory abnormalities in the liver, kidney function or platelet counts and no clinically significant changes in vital signs or ECGs in any cohort studied.

The Phase 2 study was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. A total of 114 patients with established cardiovascular disease (CVD), or being at risk for CVD, with fasting TG levels of ≥ 200 mg/dL and ≤ 500 mg/dL, and on standard-of-care preventative therapy for their known CVD risk factors were randomly assigned to 1 of the 4 parallel dosing cohorts, with each cohort having a 4:1 ratio to receive ISIS 678354 or matching volume of placebo, respectively, by SC injection for up to 12 months. The study evaluated 3 different doses of ISIS 678354: 10, 15, and 50 mg, and 3 different dosing regimens: weekly, every 2 weeks, and every 4 weeks (Q4W). The range of dosing covered the equivalent monthly drug exposure of 10 mg to 50 mg. Treatment duration was 6 to 12 months. The treatment portion of the study was complete when the last patient reached 6 months of exposure. All patients then entered a 13-week Post-Treatment Follow-up Period.

The primary efficacy analysis for the primary endpoint was the pairwise comparison of percent change from Baseline to the primary analysis time point in fasting TG between ISIS 678354-treated groups and pooled-placebo group. The primary efficacy analysis time point

was at Week 25 for patients who received every 4-week dosing and at Week 27 for patients who received every 2-week or weekly dosing.

Mean (95%CI) exposure to ISIS 678354 was 243.7 (222, 265) days. Treatment compliance was high (over 90%) in all treatment groups. Mean (standard deviation [SD]) baseline TG level for all 114 randomized patients was 284.7 (85.10) mg/dL, almost 2 times exceeding upper normal level of 149 mg/dL.

The study met the primary efficacy endpoint. Significant reductions in fasting TG levels from Baseline to the primary analysis time point were observed in all ISIS 678354-treated groups compared to placebo. The highest dose group (50 mg Q4W) achieved mean 62% reduction from Baseline in fasting TG levels compared to placebo, associated with mean 74% reduction from Baseline in apoC-III levels. The proportion of patients achieving normal fasting TG levels < 150 mg/dL showed a significant, dose-dependent increase in all ISIS 678354 treated groups with over 90% (20/22) patients treated with the highest dose of 50 mg Q4W vs. only 4.2% (1/24) patients treated with placebo achieving this threshold.

ISIS 678354 was well-tolerated and there were no safety concerns. Overall incidence and severity of treatment-emergent adverse event (TEAEs) "on-treatment" (defined as period from first dose through 1 dosing interval post-last dose) were comparable between the pooled placebo group and the pooled ISIS 678354 group. Majority of TEAEs were mild, and none of severe TEAEs was considered related to the Study Drug. The most frequently reported TEAE in the pooled ISIS 678354 group was injection site erythema (15.6%). Treatment emergent SAEs were experienced by 4.2% patients in the placebo group and 10.0% patients in the pooled ISIS 678354 group, none of them was considered related to the Study Drug. Treatment discontinuations due to TEAEs were very infrequent (overall 3 patients), and well-balanced between the pooled placebo group (4.2%) and the pooled ISIS 678354 group (2.2%).

There was 1 death on the study in 15 mg Q2W ISIS 678354 group: patient with advanced CVD and other medical history including coronary artery disease (with ST-elevation MI, CABG, multiple, 10 in total, stent placement), congestive heart failure, aortic stenosis, carotid artery disease, and type 2 diabetes mellitus, died at home, no autopsy performed, death was considered as "heart related".

ISIS 678354 was well-tolerated, there was low incidence of predominantly mild injection site reactions (12.2% vs. 4.2%), and flu-like reactions (8.9% vs. 8.3%) in patients treated with ISIS 678354 compared to placebo, respectively.

No dose- or time-dependent changes in platelet count were observed, and no patient had a confirmed platelet count < 100,000/mm^3. The incidence of minor bleeding events was comparable between the pooled placebo group (20.8%) and the pooled ISIS 678354 group (12.2%). No patient met any liver monitoring rules including increase in ALT or AST > 3 × ULN, or > 2× baseline (if baseline > × ULN). The incidence of patients meeting any renal monitoring rules (decrease from Baseline in Estimated GFR [eGFR] > 25%, increase in serum creatinine > 0.3 mg/dL, urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio, (UPCR) > 500 mg/g) was comparable between the pooled placebo group (20.8%) and the pooled ISIS 678354 group (17.8%).

Treatment with AKCEA-APOCIII-L_{Rx} was not associated with any clinically significant changes in other laboratory parameters (including coagulation panel, and inflammatory marker, hsCRP), vital signs, or ECG parameters.

2.4. Rationale for Dose and Schedule of Administration

The starting dose and dosing regimens selected for this study are 50 mg or 80 mg every 4 weeks, which is supported by both the cumulative nonclinical data available to date and the Phase 1 and Phase 2 clinical data, as well as the medical need for maximal TG reduction for the highest proportion of FCS patients to get below the pancreatitis threshold of 750 mg/dL. The APPROACH trial demonstrated that volanesorsen mediated lowering of plasma apolipoprotein C-III levels in subjects with FCS effectively lowered plasma TGs below the threshold of 750 mg/dL that has been associated with TG-induced acute pancreatitis (Berglund et al. 2012; Brown et al. 2012; Scherer et al. 2014; Valdivielso et al. 2014; Brahm and Hegele 2015; Jacobson et al. 2015; Catapano et al. 2016; Witztum et al. 2019). Based on preclinical pharmacodynamic data with ISIS 678354, a dose of 80 mg will likely maintain TG levels below 750 mg/dL in a statistically significant number of subjects. This opportunity to achieve a TG level below 750 mg/dL will help maximize the opportunity to provide a potential impact on the risk of pancreatitis.

In nonclinical studies, ISIS 678354 demonstrated good safety profiles in rodents and monkeys. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III. In the monkey, the No Observed Adverse Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. The safety margins between the NOAEL in monkeys and the clinically relevant exposure are based on cumulative plasma AUC measurements (Yu et al. 2015) or mg/kg scaling (FDA 2005; Geary et al. 1997). The NOAEL in monkeys was determined to be 6 mg/kg/wk (1680 mg/month HED assuming 70 kg human body weight; $AUC_{0\text{-}48}$: 141 µg·h/mL). This NOAEL is approximately 21-fold above the current highest proposed clinical dose (80 mg/month: estimated $AUC_{0\text{-}tau}$: 6.7 µg·h/mL). Clinical safety data to date suggest that ISIS 678354 has been well-tolerated at dose levels up to 30 mg every week (equivalent to 120 mg every 4 weeks) in patients with high TGs with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 1 and Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (Phase 1: 10 mg, 30 mg, 60 mg, 90 mg, and 120 mg single dose, and 15 mg and 30 mg per week for 6 weeks (i.e., 60 mg and 120 mg cumulative monthly equivalents, respectively), and 60 mg every 4-weeks for 13 weeks. Phase 2: 10 mg and 50 mg every 4 weeks, 15 mg every 2 weeks, and 10 mg every week, all for at least 6 months and up to 1 year).

Analysis of the cohorts in which ISIS 678354 was studied at different dose levels demonstrates dose-dependent pharmacology with respect to pharmacodynamic effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 10 mg to 120 mg per month equivalent dose range as compared to placebo. Considering the medical need for FCS patients with extremely high TG levels, often > 2000 mg/dL, achieving a maximal TG reduction over 70%, the level of reduction observed for volanesorsen at 300 mg every week dosing, is considered sufficient and necessary for ISIS 678354 to prevent the risk of acute

pancreatitis. Population PK/PD model-based simulations for a population of FCS patients predicted 70% reduction in TGs and 86% reduction in apo-CIII for 80 mg every 4-week dosing.

In addition to the nonclinical and clinical experience of ISIS 678354, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified, $GalNAc_3$-conjugated ASOs that have been safely administered SC in multiple clinical studies at doses up to 120 mg weekly for 12 weeks (ClinicalTrials.gov NCT03020745) and 20 mg weekly for up to 51 weeks (Tsimikas et al. 2020). The most advanced $GalNAc_3$-conjugated ASO (ISIS 681257; NVS TQJ230) of similar chemistry has entered into a large Cardiovascular Outcome Trial (HORIZON, NCT04023552) of 7600 subjects to be treated for a median of 4 years at a once-monthly dose of 80 mg every 4-week dosing. Cumulative safety and tolerability data from the platform as well as the preclinical and clinical experience for ISIS 678354 are supportive of this dose and dosing frequency (Crooke et al. 2018). Patients with FCS will require chronic treatment and therefore an every 4-week dosing regimen may provide advantages over weekly dosing in terms of convenience and compliance for patients.

2.5. Benefit-Risk Assessment

2.5.1. Overall Assessment of Benefit:Risk

The benefits of treatment of ISIS 678354 are currently unknown. Due to its mechanism of action, ISIS 678354 has the potential to be efficacious for the treatment of patients with FCS.

No specific risks have been identified with ISIS 678354 in the Phase 1 (678354-CS1) or Phase 2 (678354-CS2) studies. The conjugated nature of ISIS 678354 allows specific targeting of ASO to hepatocytes so, that for similar hepatocyte exposure, reduced exposure to both non-parenchymal liver cells and systemic exposure has the potential to lower apoC-III and TGs with an enhanced tolerability profile over the parent molecule, ISIS 304801. Consequently, platelet count decreases observed with the much higher doses of the unconjugated parent molecule are not anticipated to occur at the dose tested in this study.

Nevertheless, regular monitoring of platelet counts, liver chemistry, and renal function, and stopping rules will be included in the clinical study as described in Section 8.5 and Section 8.6.

Taking into account the measures implemented to minimize risk to patients participating in this study, the potential risks identified in association with ISIS 678354 are justified by the anticipated benefits that may be afforded to patients with FCS.

Detailed information concerning the benefit-risk assessment of ISIS 678354 can be found in the Investigator's Brochure.

2.5.2. Additional Risks During the COVID-19 Pandemic

Patients treated for hyperlipidemia should continue their regular regimen of diet and lifestyle measures and should also continue any approved pharmaceutical interventions for lipid lowering as no risks have been identified that would cause termination of treatment during the COVID-19 Pandemic (Iqbal et al. 2020) at this time.

There could be risk however, for patients who are participating in a clinical trial such as ISIS 678354. There may be risks to patients traveling to research sites. Sites should follow their

specific regional guidance (i.e., institutional, local, state, federal, country-level, as applicable) with regard to receiving patients for clinical trials. Visits should continue as long as it is deemed safe to do so. Provision will be available for patients to be treated or evaluated in their homes by a home healthcare professional. Additional mitigation steps and a study pause may be necessary as conditions warrant. If a study patient becomes infected with COVID-19 or develop COVID-19-related symptoms, the patient should notify the study staff/Investigator and notify their treating Physician that they are participating in a clinical trial with ISIS 678354.

3. EXPERIMENTAL PLAN

3.1. Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study. Eligible patients will enter an approximately 4-week, but no more than 8-week, Screening Period that includes an at least 2-week Diet Stabilization/Run-In Period for patients not already on a stable diet, and an approximately 2-week Qualification Period. Following qualification, approximately 60 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 2:1 to receive ISIS 678354 or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of ISIS 678354 once every 4 weeks or matching volume of placebo (0.5 mL) Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg ISIS 678354 once every 4 weeks or matching volume of placebo (0.8 mL) Weeks 1-49 of the Treatment Period. Randomization will be stratified by (1) prior history of pancreatitis (within 10 years prior to Screening) and (2) previous treatment with volanesorsen. 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. Following the Week 53 visit, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the institutional review board/independent ethics committee (IRB/IEC) and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post-Treatment Evaluation Period. The primary endpoint for the study will be evaluated after the last patient has completed the Week 53/ET visit and will be based on the percent change in fasting TG from Baseline at the primary analysis time point (Month 6).

The patients, Investigators, study staff, and the Sponsor are to remain blinded to lipid data (central and local) starting after the first dose on Day 1 then throughout the remainder of the study.

3.2. Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3. Number of Patients

Approximately 60 patients are planned to be enrolled in this study.

3.4. Overall Study Duration and Follow-up

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

- An approximately 4-week, but no more than 8-week, Screening Period including a Diet Stabilization Period of at least 2 weeks and an approximately 2-week Qualification Period (patients on stable diet, for optimal control of TGs and disease management, known to the Investigator and followed at the site may go from Screening to Qualification without the Diet Run-In Period)
- A 53-week Treatment Period during which Study Drug will be administered as a once every 4-week SC injection (Week 1 through Week 49)
- A 13-week Post-Treatment Evaluation Period or transition to OLE Study

Please refer to the Schedule of Procedures in Appendix A.

3.4.1. Screening

A period of up to 8 weeks is given to complete the screening and baseline assessments outlined in the Schedule of Procedures in Appendix A.

3.4.2. Treatment Period

The Treatment Period is 53 weeks. Eligible patients will have assessments at specified intervals throughout the 53-week Treatment Period as outline in the Schedule of Procedures in Appendix A. During the Treatment Period, Study Drug is administered by SC injection once every 4 weeks.

3.4.3. Post-Treatment Period

The Post-Treatment Follow-up Period is 13 weeks with assessments as outline in the Schedule of Procedures in Appendix A.

Alternatively, following the Week 53 visit, eligible patients may elect to enroll in the OLE study pending study approval of this proposed study by the IRB/IEC and the appropriate regulatory authority.

3.5. End-of-Study

The End-of-Study is defined as last patient, last visit.

For individual patients, End-of-Study is defined as completion of their last study visit.

3.6. Data and Safety Monitoring Board or Independent Data Monitoring Committee

An independent Data and Safety Monitoring Board (DSMB) consisting of expertise in medical specialties relevant to the safety of ASO drugs (hematology, hepatology, and nephrology) will be assembled to review safety, tolerability and efficacy (as needed) data collected on ISIS 678354 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 678354, 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 and Statistical Analysis Plan (SAP).

3.7. Allowances in the Circumstance of a Public Health Emergency

If an investigative site or the clinical trial patients associated with that site experience a public health emergency, such as a pandemic, then throughout that time the following changes to what is written elsewhere in this protocol are permissible, at the discretion of the Investigator, provided that all ICH, GCP, and regulatory requirements associated with the study are still upheld. These allowances may be implemented at any stage of the study: Screening Period, Treatment Period, and Post-Treatment Period. What is considered a public health emergency is based on circumstances and procedures at the site, and the judgment of the Investigator. The time at which a public health emergency has resolved to sufficient extent such that these allowances are no longer applicable is based on the judgment of the Investigator in consultation with the Medical Monitor.

- **Remote assessments and at-home visits**: Even when an investigative site remains open to clinical trial patients coming on site, social distancing strategies may result in some patients being unwilling or unable to attend protocol-specific clinic visits. For such reasons, scheduled clinic visits may be replaced by remote assessments (via video conference or telephone call) or at-home visits or a combination, provided that these are properly documented. This may be accomplished by at-home visits by Study Center staff or home healthcare providers, with incorporation of videoconference or telephone assessments by Study Center staff or designee.
- **Randomization**: When a patient is found to be eligible for the study, the decision regarding if and when the patient will be randomized is based on the judgment of the Investigator in consultation with the Medical Monitor. Randomization may be delayed by up to 1 month without rescreening.
- **Safety assessments**: Every effort should be made to continue performing safety assessments on schedule. This may require remote assessments (e.g., for adverse events and concomitant medications) by Study Center staff, and it may require at home visits (e.g., for blood draws, urine samples, physical examination, vital signs) by Study Center staff or home healthcare providers. Which safety assessments are considered critical, for example to support a decision on whether to administer the next scheduled dose of Study Drug to a patient, is to be determined on a case-by case basis by the Investigator in consultation with the Medical Monitor.
- **Reporting of protocol deviations**: All protocol deviations that are caused by a public health emergency should be documented as such; for example, include in the description of the protocol deviation that it is related to COVID-19. The impact such protocol deviations had on the study is to be summarized in the clinical study report. This summary is considered sufficient notification of the EC / IRB for minor protocol deviations that were caused by a public health emergency.
- **Laboratory assessments associated with primary or secondary endpoints**: Every effort should be made to perform the assessments on schedule.

- **To support Study Drug administration at home**, delivery of Study Drug to the patient may be undertaken at the discretion of the Investigator, based on local and regional regulations for transporting investigational product.
- **Immunization of patients with a vaccine for COVID-19, or antiviral treatments under an emergency use authorization for COVID-19,** outside of a clinical trial, may occur while patients are on study, however it is preferable that a separation of at least 7 days occurs between administration of the vaccine or antiviral and administration of Study Drug. Adjustment of the schedule for monthly administration of Study Drug may be considered in order to achieve this separation. In addition, Study Drug should not be injected into the same anatomical location as the vaccine for COVID-19.

4. PATIENT ENROLLMENT

4.1. Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written IEC/IRB approval of the protocol, informed consent form, and all other patient directed information and/or recruitment material.

Patients or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. 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. The screening number and patient identification number must remain constant throughout the entire trial. Patients may be re-screened 1 time in order to determine eligibility. 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.

4.2. Randomization

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

Using an Interactive Response Technology (IRT) system, eligible patients will be randomized 1:1 to Cohort A or Cohort B and each cohort further randomized 2:1 to receive ISIS 678354 or placebo. Patients will be stratified for:

- Prior history of pancreatitis within 10 years prior to Screening* vs. no history of pancreatitis or no history within 10 years prior to Screening
- Previous treatment with volanesorsen (Yes vs. No)

* History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made.

The randomization lists will be prepared by an independent external vendor.

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

4.4. Unblinding of Treatment Assignment

The Sponsor and all patients, monitors, and Study Center personnel related to the study will be blinded throughout the study until all patients have completed the study and the database has been locked. Representatives from the Sponsor may be unblinded after the last patient has completed the end of the treatment period (Week 53/ET) as described in the Unblinding Plan. Those Sponsor representatives will no longer be involved in the conduct of the study after they have been unblinded.

However, if a patient has suffered an SAE (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient using the IRT.

The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's designated vendor. In addition, all suspected unexpected serious adverse reaction (SUSARs) will be unblinded by the Sponsor or designee for the purpose of unblinded regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendix A) prior to unblinding, as knowledge of the treatment arm could influence subject assessment.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 8 weeks of Study Day 1 or at the time point specified in the individual eligibility criterion listed.

5.1. Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Aged ≥ 18 years at the time of informed consent
3. A diagnosis of Familial Chylomicronemia Syndrome (type 1 Hyperlipoproteinemia) by documentation of confirmed homozygote, compound heterozygote or double heterozygote for loss-of-function mutations in type 1-causing genes (such as *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, *GPD1*, or *LMF1*)
4. Fasting TG ≥ 880 mg/dL (10 mmol/L) at Screening. If the fasting TG is < 880 mg/dL up to 2 additional tests may be performed with any single test used to qualify

5. History of pancreatitis (defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made) within 10 years prior to Screening. Patients without a recorded history of pancreatitis, or no recorded history within 10 years prior to Screening, are also eligible but their enrollment will be capped at 35% (i.e., ≤ 21 of the 60 planned patients)
6. Willing to follow a diet comprising ≤ 20g fat per day during the study
7. Willing to complete all Patient Reported Outcome assessments throughout the study as described in Section 6.2.5
8. Satisfy the following:
    a. Females: must be non-pregnant and non-lactating and either:
        i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
        ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved)
        iii. Abstinent* or
        iv. If engaged in sexual relations of child-bearing potential, agree to use a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 17 weeks after the last dose of Study Drug (ISIS 678354 or placebo)
    b. Males: Surgically sterile, abstinent*, or if engaged in sexual relations with a female of childbearing potential, patient is using a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 17 weeks after the last dose of Study Drug (ISIS 678354 or placebo)

    * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception
9. Atypical antipsychotic medications (e.g., olanzapine and clozapine) will be allowed if on a stable dose for at least 3 months prior to Screening and dose and regimen expected to remain constant through the end of their participation in this study
10. The following concomitant medications will be allowed if on a stable dose for at least 4 weeks prior to Screening and dose and regimen expected to remain constant through the end of their participation in this study (occasional or intermittent use of over-the-counter [OTC] medications will be allowed at Investigator's discretion):
    a. Statins, omega-3 fatty acids (prescription and OTC), fibrates, or other lipid-lowering medications. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand through the end of the study
    b. Antidiabetic medications

c. Antihypertensive medications
d. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) and regular clinical monitoring is performed
e. Tamoxifen, estrogens or progestins

5.2. Exclusion Criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Active pancreatitis within 4 weeks prior to Screening
3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion
   a. Platelet count < 100K/mm^3 at Screening or Qualification. If the platelet count is < 100K/mm^3 up to 2 additional tests may be performed to qualify at both Screening and Qualification.
   b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3.0 × upper limit of normal (ULN)
   c. Total bilirubin > ULN unless due to Gilbert's syndrome
   d. Estimated GFR < 45 mL/min/1.73 m^2 [as determined by the CKD-EPI formula for creatinine clearance; (Levey et al. 2009)]
   e. Urine protein/creatinine ratio (UPCR) ≥ 500 mg/g, or urine albumin/creatinine (UACR) ratio ≥ 300 mg/g
4. Uncontrolled arterial hypertension (BP > 160/100 mm Hg)
5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening
6. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 or active Covid-19 infection with or without therapy that will not be resolved by Study Day 1
7. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor
8. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor
9. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening

10. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
11. Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening, or 5 half-lives, whichever is longer. This exclusion does not apply to vaccines
12. Concomitant medication/procedure restrictions:
    a. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening and during the study unless approved by the Sponsor Medical Monitor
    b. Plasma apheresis within 4 weeks prior to Screening or planned during the study
13. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
14. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1. Study Schedule

All required study procedures are outlined in Appendix A, Appendix B and Appendix C.

6.1.1. Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. An up to 8-week period is provided for completing screening assessments and determining patient eligibility for the study. Abnormal screening results may be re-tested once for determination of patient eligibility after consultation with the Sponsor Medical Monitor. Patients may be re-screened 1 time in order to determine eligibility.

During the Screening Period, patients will undergo a medical history and physical examination including vital signs, 12-lead ECG and have blood and urine samples taken for clinical laboratory testing. Patients will be screened for HIV, hepatitis B and hepatitis C.

As part of the Screening Period, patients not already on a stable diet will have 2 weeks of diet run-in, followed by a qualification visit, during which final eligibility assessments will be performed. Patients on a stable diet, known to the Investigator and followed at the site, may go from Screening to qualification without a 2-week diet run-in. At the qualification visit, TGs will be measured.

Race & Ethnicity data will be collected as part of the demographic information for all screened patients during the Screening Period.

6.1.2. Treatment Period

The Treatment Period is defined as the time between the first and the last dose of Study Drug plus 1 dosing interval. Patients will receive Study Drug administered by SC injection once every 4 weeks for 49 weeks. Collection and measurement of vital signs, physical examination results, ECGs, laboratory parameters (Appendix B), ISIS 678354 plasma concentrations, anti-drug antibody (ADA) and biomarker samples, patient reported outcome assessments, AEs and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Appendix A.

6.1.3. Post-Treatment Period

After completion of the Week 53 visit assessments, patients will enter the 13-week Post-Treatment Follow-up Period. Alternatively, after completion of the Week 53 visit assessments, eligible patients may elect to receive ISIS 678354 in the OLE study, pending study approval by the IRB/IEC and the appropriate regulatory authority. In this case, patients will need to sign the IRB/IEC approved informed consent. Patients who complete Study Visit Week 53, and meet eligibility requirements, may start the Treatment Period in the OLE study any time after the Week 53 visit and, if relevant, discontinue participation in the CS3 Post-Treatment Evaluation Period.

6.2. Additional Study Assessments

6.2.1. Laboratory Assessments

Laboratory analyte samples will be collected throughout the study as per the Schedule of Procedures in Appendix A. A list of these analytes is contained in Appendix B.

Routine blood chemistry and lipid samples should be taken after fasting for at least 10 hours and preferably not more than 12 hours. Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status, but no later than 7 days after the initial result is obtained. During preparation for fasting samples, the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

If tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood or urine specimen should be re-drawn as soon as possible (ideally within 1 week).

While on treatment, hematology samples will be collected at least every 14 days (± 2 days). In the event that a hematology sample is unreportable (e.g., due to hemolyzed or clumped blood samples), patient dosing cannot continue until another sample (central or local) is repeated and determined not to have met a platelet stopping rule.

Investigators may, at their discretion, test specific laboratory parameters which may be prone to clotting, clumping or hemolysis (e.g., hematology samples) at their local laboratory, in addition to the required central laboratory samples. In these instances, the local laboratory results should be recorded by the site into the electronic database. Assays which are blinded should not be locally tested and recorded into the database (e.g., lipid panel).

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

While on treatment, blood and urine samples for renal function testing will also be collected every 14 days (± 2 days) and sent to the central laboratory for analysis for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period per Section 8.5.2.

While on treatment, liver function testing will also be collected every 14 days (± 2 days) and sent to the central laboratory for analysis for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period per Section 8.5.1.

All lab samples are to be sent to the central laboratory by overnight courier and processed. Lab alerts issued will indicate the applicable protocol section to facilitate review and will be immediately and simultaneously sent by email to the Investigator, the Sponsor and the CRO Medical Monitors, the Sponsor Drug Safety Physician, and the Clinical Trial Manager (CTM), and should be received by them within 2 days from sample collection. All lab sample results from the site's local laboratories are received by the Study Center staff per the local laboratories' standard reporting time, and should be entered as soon as possible (ideally within 1 week) into the electronic Case Report Form (eCRF) to inform the Sponsor and CRO study monitoring teams.

All platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the count has not met a dose interruption or stopping rule. Any case of platelet count reduction to levels below 50,000/mm^3 accompanied by a major bleeding (MB) event or clinically relevant non-major bleeding (CRNMB) event, or platelet count of < 25,000/mm^3 independent of a MB or CRNMB event, is considered an AE of special interest (AESI) and must be reported in an expedited fashion to the Sponsor as per Section 9.3.4 and Section 9.4.1.

All liver and renal function tests must also be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the result has not met the stopping rule.

All lab alerts received, including those related to platelet, liver, or renal function monitoring/stopping rules, are also reviewed promptly by the Sponsor and the CRO Medical Monitors who will agree on actions to be taken. Within 24 hours of receiving an actionable lab alert the CRO Medical Monitor will communicate instructions to the Investigator and the study personnel by emailing them the Safety Surveillance Form that needs to be completed and signed by the Investigator/study personnel and promptly returned to the Sponsor and CRO Medical Monitor. In urgent cases, such as platelets results below 50,000/mm^3, or liver or renal test results reaching a critical stopping rule, the Investigator must also be contacted by phone.

Further information on safety monitoring and actions to be taken by the Study Investigator in the event of reduced platelet count are provided in Section 8.5.3 and Section 8.6.3.

6.2.2. Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, BP, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at Screening.

6.2.3. Electrocardiography

Electrocardiography will be conducted at Screening, Day 1 (prior to the first dose of Study Drug), and again during the Treatment Period and at each post-treatment follow-up visit as outlined in Appendix A.

Electrocardiography will be recorded after the patient has been resting in a supine position for at least 5 minutes. Electrocardiography will be performed in triplicate.

6.2.4. Pharmacokinetic Sampling

Blood samples for the determination of plasma ISIS 678354 concentrations will be collected prior to dosing on Day 1 and at various times throughout the treatment and Post-Treatment Follow-up Period as noted in the table in Appendix C.

6.2.5. Patient Reported Outcomes Assessments

All patients are to complete the FCS Symptoms Two Week Recall at Screening and the FCS Symptoms and diet questionnaire on a daily basis for FCS symptoms/diet (minimum of 4 daily assessments per week) and every 4 weeks for FCS Impacts, and complete the PROMIS Adult Short Form v1.1 (Pain Interference 8a) every 4 weeks, for the duration of the study as outlined in Appendix A. Health-related quality of life (as measured by the PROMIS 29+2 Profile vs. 2.1) and an optional PROMIS® Short Form v2.0 – Cognitive Function 4a will be assessed at Baseline, 3 months, 6 months and end of study. Patient-reported global impression of severity (PGIS) will be administered at Baseline and every 4 weeks; the patient-reported global impression of change (PGIC) at 6 months and end of study. Patient-reported global impression of severity and PGIC are administered for purposes of PRO validation and estimation of minimal important difference (MID).

6.2.6. Pancreatitis Medical History

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 10 years prior to Screening and information relating to these events, occurring up to 5 years prior to Screening, will be collected for independent adjudication.

6.3. Restriction on the Lifestyle of Patients

6.3.1. Prevention of Pregnancy

Every effort must be made to prevent pregnancy throughout the entire study. All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or practice highly effective contraception from the time of signing the informed consent form until at least 17 weeks after their last dose of Study Drug.

For the purposes of this study, females of childbearing potential are defined as any female who has experienced menarche, and who does not meet one of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post-hysterectomy

For the purposes of the study, highly effective contraception is defined as follows:

For male patients:

- Highly effective male contraception includes a vasectomy with negative semen analysis at follow-up, surgically sterile via bilateral orchidectomy, or the non-pregnant female partner of child-bearing potential uses a highly effective contraceptive method (defined below)

For female patients and female partners of male patients, highly effective female contraception methods comprise:

- Surgical sterilization (e.g., bilateral tubal occlusion hysterectomy, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing, or progestogen-only), intrauterine contraception device or intrauterine hormone-releasing system (IUS), or the male partner uses highly effective contraceptive method (defined above).

†**Note:** Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

Note: A female condom and a male condom should not be used together as friction between the 2 can result in either or both products failing.

Note: Male patients with partners who are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

6.3.2. Other Requirements

All patients will be required to fast for at least 10 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event based on Atlanta Classification (Banks et al. 2013). If serum lipase and/or amylase activity is less than 3 × ULN, imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1. ISIS 678354 or Placebo

Study Drug (ISIS 678354 or Placebo) characteristics are listed in Table 1.

The Study Drug is contained in 2-mL stoppered glass vials. The Study Drug and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug must be stored securely at 2–8 °Celsius and protected from light.

Olezarsen vials contain 100 mg/mL olezarsen in Water for Injection. Additionally, phosphate buffer and sodium chloride are added to control the pH of the solution and tonicity, respectively. The target pH is 7.4 and tonicity is within a physiologically acceptable range.

Placebo vials contain 0.9% sodium chloride in Water for Injection. Riboflavin is added for color similarity of placebo vials to olezarsen vials.

Table 1: Study Drug Characteristics

Study Drug	**ISIS 678354**	**Placebo**
Strength	100 mg/mL	Not Applicable
Volume/Formulation	0.8 mL solution per vial	0.8 mL solution per vial
Route of Administration	Subcutaneous	Subcutaneous

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of Study Drug supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1. Study Drug Administration

For each individual patient in the 50 mg cohort (Cohort A), Study Drug will be administered SC as a single 0.5 mL injection once every 4 weeks for Weeks 1-49 for a total of 13 doses. For each individual patient in the 80 mg cohort (Cohort B), Study Drug will be administered SC as a single 0.8 mL injection once every 4 weeks for Weeks 1-49 for a total of 13 doses. Self-administration will be allowed after appropriate training of patient and/or caregiver.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for Study Drug preparation, administration and patient observation post-Study Drug administration.

8.2. Other Protocol-Required Drugs

No other Study Drug treatments are required by the protocol.

8.3. Other Protocol-Required Treatment Procedures

No other treatment procedures are required by the protocol.

8.4. Treatment Precautions

No specific treatment precautions are required.

8.5. Safety Monitoring Rules

Stopping rules are described below in Section 8.6.

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

- For the purposes of safety monitoring Baseline is defined as the average of the Day 1 pre-dose assessment and the last measurement prior to Day 1.
- In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.
- In case of discrepancy between the test results from 2 sources, such as between the central and local lab, safety-mandated action must be initiated based on the more critical (lower or higher, as relevant) of the 2 values.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the clinical laboratory results meeting any of the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the

initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days but no later than 7 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drug.

Re-dosing Guidance: In the event the initial laboratory result meets a stopping criterion, the results from the retest **must be available and reviewed by a Medical Monitor** prior to administration of the next dose of Study Drug (ISIS 678354 or placebo). In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to at which dose Study Drug should be restarted, and whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Section 8.6.1 through Section 8.6.3) are met, the patient will be permanently discontinued from further treatment with Study Drug (ISIS 678354 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

The Investigator may interrupt or permanently discontinue study treatment for any medical reason including changes in clinical laboratory results.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above.

All patients will have liver chemistry tests monitored every 14 days (± 2 days) for the first 3 months of the Treatment Period, and monthly thereafter during the Treatment Period. Upon completion of the study Treatment Period, liver chemistry tests should be monitored as per visit schedule in Appendix A.

In the event of appearance of symptoms or signs of hepatic injury (jaundice, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, abnormal bleeding or bruising, or eosinophilia > ULN) liver enzymes and bilirubin should be tested as soon as possible (ideally within 3 days). Testing at a lab that is local to the patient is permissible for this purpose.

In the event of an ALT or AST measurement that is > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described in Section 8.5.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase [ALP], INR and total bilirubin) retested at least once weekly until ALT and AST levels become ≤ 1.2 × ULN or 1.2 × baseline if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), the following evaluations should be performed:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, cytomegalovirus (CMV) IgM, and EBV antibody panel)
- Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach ≥ 5 × ULN.

The Study Drug must be interrupted until all evaluations and consultation with the Sponsor Medical Monitor is complete.

Patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN) without an alternative explanation, and not meeting any of the Stopping Rules for liver chemistry elevations described in Section 8.6.1, must have Study Drug dose permanently reduced to 50 mg, if on an 80-mg dose. Patients on 50 mg should remain on the 50-mg dose.

All routine liver function test results will be reviewed on an ongoing basis at the weekly safety review by the Sponsor Medical Monitor.

All lab alerts for abnormal liver function tests must be promptly reviewed by the Investigator (within 48 hours of receipt) and Medical Monitor(s) (within 24 hours of receipt) as described in Section 6.2.1.

Lab alerts for abnormal liver chemistry tests will be issued for: 1) ALT or AST > 3 × ULN; 2) ALT or AST > 2 × baseline; 3) total bilirubin > ULN; 4) ALP > ULN. These alert levels are set to anticipate the risk of a combined elevation of aminotransferases and bilirubin as per the FDA Guidance referenced in Section 8.5.1 above.

8.5.2. Safety Monitoring for Renal Function

While on treatment, all patients will have renal function tests monitored every 14 days (± 2 days) for the first 3 months of the Treatment Period, and monthly thereafter during the Treatment Period. Upon completion of the study Treatment Period, renal function tests should be monitored as per visit schedule in Appendix A.

In the event of appearance of symptoms or signs consistent with renal dysfunction such as hematuria, polyuria, anuria, flank pain, new-onset hypertension, nausea and/or anorexia, renal

function should be tested as soon as possible (ideally within 3 days). Testing at a lab that is local to the patient is permissible for this purpose.

Renal function surveillance will include serum creatinine and urinalysis including UACR, UPCR, urinary red blood cells (RBC). The assessment of serum creatinine and urinalysis more frequently than every 14 days will be guided by consultation with a local nephrologist.

All renal function test results will be reviewed on an ongoing basis by the Medical Monitor.

All results of renal function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.2.

If any of the below criteria are met, an alert will be issued and treatment with Study Drug should immediately be interrupted, and the Study Medical Monitor should be informed. In addition, the result should be confirmed as soon as possible (as described in Section 8.5), but no later than 7 days after the initial event.

- eGFR (by CKD-EPI formula) decrease from Baseline > 25%
- Urine albumin/creatinine ratio (UACR) > 300 mg/g, or > 50% Baseline whichever is greater
- UPCR > 500 mg/g, or > 50% Baseline whichever is greater

If the confirmatory test is negative (i.e., repeat sample taken with 7 days is within normal limits), the patient may continue treatment with Study Drug upon consultation with the Medical Monitor. If results from additional testing confirm the initial abnormal lab result, the site will obtain any additional lab assessments necessary to determine any alternative etiologies that may account for the abnormal result, upon consultation with the Medical Monitor.

The Investigator should also review the patient's concomitant medications for potentially nephrotoxic agents, and, with the results of these evaluations, review any decision to continue or discontinue the patient in consultation with the Medical Monitor. Any decision taken by the Investigator to discontinue Study Drug will be made taken into account all available and relevant data. In addition, the decision to discontinue Study Drug may also be based on lesser changes in these parameters observed in isolation or in association with other renal-related abnormalities.

Further instruction regarding treatment interruption and/or permanent stopping of Study Drug can be found in Section 8.6.2.

8.5.3. Safety Monitoring for Platelet Count Results

All patients will have PLT counts monitored at least every 14 days (± 2 days) for the duration of the study Treatment Period, and at all post-treatment follow-up visits, and must not receive Study Drug without an interpretable PLT count result in the prior 14 days. Upon completion of the study Treatment Period, PLTs will be monitored at least every 14 days (± 2 days) for the first 6 weeks and then at 8 and 13 weeks Post-End of Treatment Period (as per visit schedule).

All PLT count results must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the count has not met a dose interruption or stopping rule. Actions to be taken in the event of reduced PLT count are shown in Table 2.

Table 2: Actions in Patients with Low Platelet Count

Platelet Count on Rx	**Drug Dose**	**Monitoring**
Normal range, ≥ 140K/mm^3	No action	Monitor every 14 days (± 2 days)
Below values to be confirmed ideally within 3 days but no later than 7 days	**If PLT count is confirmed, follow dosing guidance below:**	**If PLT count is confirmed, follow monitoring guidance below:**
≥ 100K to < 140K/mm^3	No action	Monitor every 2 weeks
≥ 75K to < 100K/mm^3	**Discussion with Medical Monitor*****	Closer observation; monitor every week**
≥ 50K to < 75K/mm^3	Pause dosing. When ≥ 2 successive PLT count values return to ≥ 100K/mm^3 restart dosing **only if approved by Medical Monitor*****	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of anticoagulants/ antiplatelet agents/non-steroidal anti-inflammatory drug (NSAIDs)
≥ 25K to < 50K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue anticoagulants/antiplatelet agents/, NSAIDs, while PLT count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids and/or IVIG recommended****** Consider referral to hematologist Discontinue anticoagulants/antiplatelet agents/NSAIDs medication while PLT count < 50K/mm^3 if possible

* Once a patient commences every 2-week monitoring this frequency of monitoring should continue until the platelet count returns to ≥ 140K/mm^3) for 2 successive values

** Once a patient commences weekly monitoring this frequency of monitoring should continue until the platelet count returns to ≥ 100K/mm^3) for 2 successive values.

*** The suitability of the patient for reduced, interrupted and/or continued dosing will be determined by the Investigator in consultation with the Medical Monitor and will be based on factors such as the original rate of decline in the patient's PLT count, whether any bleeding events were experienced by the patient, and the speed of recovery of PLT count after interruption of dosing.

**** Recovery in platelet count may be accelerated by administration of high-dose glucocorticoids. Treatment as recommended by the American Society of Hematology (ASH) (Neunert et al. 2019) guidelines for immune thrombocytopenia (Blood Advances, 10 DECEMBER 2019, Volume 3, Number 23) includes initial therapy with either dexamethasone 40 mg per day for 4 days, or prednisone 0.5 to 2.0 mg/kg per day. Prednisolone or prednisone may be administered for up to 2 to 4 weeks with taper; alternatively, intravenous immunoglobulin (IVIG) may be administered at 0.4 g/kg/d for 5 days, or infusions of 1 g/kg/d for 1-2 days (Provan et al. 2010; 2019).

Any case of a PLT count reduction to levels below 50,000/mm^3 accompanied by a MB event or CRNMB event, or PLT count of < 25,000/mm^3 independent of a MB or CRNMB event, is considered an AESI and should be reported following the same requirements as for SAE reporting.

Table 3: Additional Lab Analyses for Patients with Platelet Count Less Than 50,000/mm^3

The following is a list of lab analyses for patients who have any occurrence of platelet count less than 50,000/mm^3. Archived samples prior to Day 1 of investigational treatment may also be analyzed in order to determine the patient's baseline conditions.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes and mean platelet volume
Total globulins: IgG and IgM
Complement: total C3, total C4, C5a
Serology for:
HBV, HCV, HIV (if not done recently for screening)
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies
Anti-ASO antibody

Note: These labs may be performed in the event of a platelet count less than 75,000/mm^3 after discussion with the Study Medical Monitor. Additional lab tests may be considered in order to ascertain potential causative conditions for significant platelet count decreases / thrombocytopenia.

8.5.4. Safety Monitoring for Bleeding Events

Patients will be evaluated for occurrence of bleeding events continuously after the start of Study Drug treatment (Day 1) up to the end of the Follow-up Period. All bleeding events are considered AEs and reported on the AE case report form.

If an event a MB or CRNMB event occurs (as defined below), the Investigator must notify the Medical Monitor (or designee) and the patient should be treated, as needed, immediately and closely monitored (vital signs, lab tests such as hemoglobin (Hb), hematocrit (HCT), and PLT count, additional visits, overnight stays and coagulation tests may be needed if deemed appropriate by the treating physician) throughout the Treatment and Post-Treatment Evaluation Periods and an (S)AE case report form will be completed. In addition, approximately 2 mL of

K2EDTA anticoagulated blood will be collected and resulting plasma must be stored allowing for a centralized assessment of ISIS 678354 concentrations.

If a minor bleeding event occurs, the Investigator should notify the Medical Monitor (or designee) and additional testing of coagulation parameters (aPTT, PT, INR), PLT count, and PLT volume may be performed.

Major bleeding is defined as 1 of the following (Schulman and Kearon 2005):

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardial, or intramuscular with compartment syndrome
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed RBCs or whole blood or a fall in Hb of 2.0 g/dL (1.24 mmol/L) or more within 24 hours

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for MB but that resulted, for example, in medical examination, intervention, or had clinical consequences for a patient (Schulman and Kearon 2005).

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epistaxis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Minor bleeding events are those that do not fulfill the criteria for MB or clinically relevant, non-major bleeding events (defined above), for example excess bruising, petechiae, gingival bleeding on brushing teeth.

8.5.5. Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs or symptoms of fever, constitutional symptoms, rash, arthralgia or joint swelling that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients who experience persistent or increasing symptoms should be tested for ADA and discussed with the Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.6. Safety Monitoring for Potential Hypersensitivity Reactions

Patients will be instructed to promptly report any signs or symptoms of potential hypersensitivity reactions that include the acute onset of the following: urticarial rash, pruritus, flushing, angioedema dyspnea, and/or acute onset hypotension, that may arise during the study. The Investigator should closely evaluate all potential causes, including concomitant illnesses.

Patients who experience symptoms of a potential hypersensitivity reaction should be tested within 15 minutes to 3 hours after onset of symptoms, or as soon as possible thereafter for:

- Tryptase
- High-sensitivity C-reactive protein (hsCRP)
- Erythrocyte sedimentation rate (ESR)
- Complement factors (C3, C4, C5a, and Bb)
- Immunoglobulin E (IgE)
- CBC with differential
- Serum chemistry
- Urinalysis
- UPCR
- Anti-drug antibody (ADA)
- Antinuclear antibody (ANA)
- Antineutrophilic cytoplasmic antibody (ANCA)

If a hypersensitivity reaction is established, Study Drug discontinuation should be recommended. The patient's symptoms should be managed per standard of care.

8.5.7. Safety Monitoring for LDL-C Elevations

Beginning at Week 27, laboratory alerts will be in place to notify the Investigator if a patient has an LDL-C > 130 mg/dL (> 100 mg/dL for patients with T2DM or CAD with Baseline LDL-C > 100 mg/dL) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.6. Stopping Rules

Monitoring rules are described above in Section 8.5.

For the purposes of stopping rules, Baseline is defined as the average of the Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1. Stopping Rules for Liver Chemistry Elevations

All cases of confirmed laboratory results meeting any of the following criteria, but having an alternative etiology such as congestive heart failure, introduction of a new drug, some identified biliary tract issues etc., must be reviewed by local hepatologist, the DSMB hepatologist, and the decision to restart the Study Drug must be made upon reaching a general agreement between consulting hepatologist, the DSMB hepatologist, and the Sponsor Medical Monitor that the alternative etiology is well supported as the likely cause, and when ALT and AST levels become

≤ 3 × ULN. **Until this evaluation is completed and a decision agreed upon, the treatment with the Study Drug will remain interrupted.**

In the event of confirmed laboratory results meeting any of the following criteria, **and the event is without an alternative explanation as discussed with the Medical Monitor,** dosing of a patient with Study Drug (ISIS 678354 or placebo) will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 × ULN, which is confirmed
2. ALT or AST > 5 × ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 × ULN or INR > 1.5
4. ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed, **and** the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2. Stopping Rules for Renal Function Test Results

In the event that the any of the renal monitoring rules summarized in Section 8.5.2 are met, treatment with Study Drug should immediately be interrupted and the abnormal result should be confirmed as soon as possible, but no later than 7 days after the initial event. In addition, upon consultation with the Medical Monitor, the site will obtain any additional lab assessments necessary to determine any alternative etiologies that may account for the abnormal result. If results from additional testing confirm the initial abnormal lab result(s) described in Section 8.5.2, and additional evaluations regarding etiology accounting for these abnormalities are completed, future treatment of the patient will be determined per the guidelines below:

- An alternative etiology is identified that may account for abnormal results
  - Patient will have treatment with Study Drug interrupted until either:
    - Lab values have returned to baseline, and/or
    - Alternative etiology has resolved/recovered, AND
    - Study Medical Monitor has approved Study Drug treatment to resume
- An alternative etiology has not been identified that may account for abnormal results:
  - Patient will be permanently withdrawn from Study Drug treatment

The follow-up schedule and frequency of renal function monitoring after the initial event will be determined by the Medical Monitor in consultation with the Investigator. The Investigator should consider consulting a local nephrologist for any change of renal function that presents a concern. If a renal biopsy is performed, a sample specimen should be made available for examination by an independent renal pathologist who has been engaged by the Sponsor to review such specimens.

8.6.3. Stopping Rule for Platelet Count Results

Actions to be taken in the event of a low PLT count are summarized in Table 2 above.

8.6.4. Stopping Rule for Bleeding Events

In the event of Major Bleeding or Clinically Relevant Non-major Bleeding (see definitions in Section 8.5.4 as assessed by the Investigator, dosing of a patient with Study Drug (ISIS 678354 or placebo) may be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined, including the suitability of the patient for resumption of dosing by the Investigator in consultation with the Medical Monitor (or designee).

8.7. Adjustment of Dose and/or Treatment Schedule

Dose adjustments for platelet count reduction must be made in accordance with Table 2 (above).

Other adjustments, including dose interruptions, and/or decreasing the dose will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

Dose adjustments should not occur unless absolutely necessary prior to the primary analysis time point (Month 6).

8.8. Discontinuation of Study Drug

A patient must permanently discontinue Study Drug treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of Study Drug
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6.1 to Section 8.6.3
- The patient experiences an AE that necessitates unblinding of the Investigator or Sponsor to the patient's treatment assignment

The reason for discontinuation of Study Drug must be recorded in the eCRF and source documentation.

8.8.1. Follow-up Visits for Early Termination from Treatment Period or Post-Treatment Follow-up Period

Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 23, 25, 27 and Weeks 51 and 53 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with Appendix A. Any patient who discontinues early from the Post-Treatment Follow-up Period should be strongly encouraged to complete follow-up study visits, procedures and observations in accordance with Appendix A.

Any patient who discontinues early from the Treatment Period or from Post-Treatment Follow-up Period should be followed as per the platelet monitoring rules shown in Table 2, Section 8.6.3 for the first 6 weeks Post-End of Treatment Period and then at 8 and 13 weeks Post-End of Treatment Period (as per visit schedule).

If a patient discontinues early from the Treatment Period and declines or is unable to participate in the above, an ET visit (Week 53 visit assessments) should be performed at the time of withdrawal, and ideally within 2 weeks from the last dose of Study Drug , and patients should start the 13-week Post-Treatment Follow-up Period to collect the study assessments in accordance with the Schedule of Procedures in Appendix A.

If the patient discontinues early from the Post-Treatment Follow-up Period and declines or is unable to participate in the above, a final visit (assessments from Week 13 of the Post-Treatment Follow-up Period) should be performed at the time of withdrawal.

8.9. Withdrawal of Patients from the Study Procedures

Patients must be withdrawn from study procedures for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol
- The patient meets any of the Exclusion Criteria (see Section 5.2) after enrolling in the study that in the opinion of the Investigator represents a safety risk to the patient

Other reasons for withdrawal of patients from study procedures might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the early termination study procedures and observations at the time of withdrawal Appendix A.

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination of study procedures and observations at the time of withdrawal (see Appendix A) and ideally within 2 weeks from the last dose of Study Drug.

8.10. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.10.1. Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including OTC medications, herbal medications and vitamin supplements) administered from the time the patient has signed the informed consent at Screening to the end of the Post-Treatment Follow-up Period.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No GLP-1 agonists, or systemic corticosteroids may be started or adjusted after screening. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, oral anticoagulants, antihypertensive medication, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between Screening and the end of the Post-Treatment Follow-up Period.

Disallowed Concomitant Procedures

Plasma apheresis is not allowed during the study.

8.11. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the eCRF by Study Center staff.

Patients or Study Center Staff will record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor and entered into the eCRF.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the applicable Ionis and/or designee SOPs throughout the conduct of the clinical trial.

9.2. Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including SUSARs per the International Conference on Harmonization (ICH) guidelines E2A and ICH GCP. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards/Independent Ethics Committees will be notified of any SAE according to applicable regulations. The DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the Study Drug (ISIS 678354 or placebo) is causally related to a reported SAE.

The Sponsor or designee will evaluate the available information for all reported SAEs and decide if there is a reasonable possibility that the Study Drug (ISIS 678354 or placebo) caused the SAE and, therefore, meets the definition of a SUSAR.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of the Study Drug (ISIS 678354 or placebo) exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Section 9.4.1 to Section 9.4.3.5.

Table 4: Expected Event for the Protocol Defined Population by Preferred Term and Expected Incidence

Preferred Term	**Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010; 2013)**
Pancreatitis associated events including the PTSs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2–0.35 events per patient year

Fatal pancreatitis associated events will be considered as unexpected and reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-Study Drug exposed population. If the aggregate analysis indicates that an event is occurring more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on a case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR, the event will be reported.

9.3. Definitions

9.3.1. Adverse Event

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.3.2. Adverse Drug Reaction and Suspected Unexpected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, ADR is defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the AE has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event

A serious AE is any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected AE that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, or spontaneous abortion/miscarriage.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; OR Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

9.3.4. Adverse Event of Special Interest

An adverse event of special interest (AESI), including both serious or non-serious events, is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate.

Adverse events of special interest are required to be reported by the Investigator to the Sponsor following the same requirements as for SAE reporting (Section 9.4.1).

For the purpose of this study there are 2 AESIs:

1. Severe reductions in platelet count < 50,000/mm^3 accompanied by a MB event or CRNMB event, or platelet count of < 25,000/mm^3 independent of a MB or CRNMB event
2. Requirement of any use of medications (such as antihistamines, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroids, etc.) as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction.

9.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

9.4.1. Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs and AESIs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's Follow-up Period. SAEs should be captured and reported electronically within Electronic Data Capture System (EDC). The SAE reporting instruction, including the fax number and email address can be found in the Investigator site file for the study.

Detailed information should be actively sought and included on electronic Follow-Up Serious Adverse Event Forms in EDC as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's Follow-up Period. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form.

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 678354 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 678354 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 678354 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests will be graded based on criteria from the CTCAE Version 5.0, November 2017 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

The severity of AEs and SAEs relating to AEs at the injection site will be graded based on criteria from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007 (refer to Appendix D).

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3. Action Taken with Study Drug

Action taken with Study Drug (ISIS 678354 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug (ISIS 678354 or placebo) administration and dose

- **Not Applicable:** SAE/AE was reported during Screening Period prior to Study Drug administration
- **Permanently Discontinued:** Study Drug was discontinued and not restarted
- **Temporarily Interrupted, Restarted:** Dosing was temporarily interrupted or delayed due to the AE and restarted
- **Reduced Dose:** Dosing was reduced to a lower dose

9.4.3.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

9.4.3.6. Follow-Up of Adverse Event

Investigator Follow-Up

During the Study Period, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the

patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to Study Drug or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification.

Investigator should follow-up, or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study patient or the female partner of male study patient until pregnancy outcome is available.

Sponsor Follow-Up

For SAEs, AESI and pregnancy cases in patients who have completed or terminated the study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit (on-site or remote access) to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.4.3.7. Adjudication Committees

All AEs and SAEs that occur during the study that are consistent with a major adverse cardiovascular event (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 episodes of acute pancreatitis or suspected pancreatitis in the 5 years prior to enrollment will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory report.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3. Dosing Errors

Study Drug (ISIS 678354 or placebo) errors (including overdose, underdose, and administration error) should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of Study Drug (ISIS 678354 or placebo) that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Should an overdose occur, the Investigator or designee should contact the Sponsor or designee within 24 hours.

9.5.4. Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours of awareness of the pregnancy outcome.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including during the Follow-up Period), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the Investigator will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if the newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may follow-up with the mother and may request access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if the newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., partner ICF may be required.

Spontaneous abortion/miscarriage is to be reported as an SAE. See Section 9.4.1 for additional information regarding SAE reporting.

10. STATISTICAL CONSIDERATIONS

10.1. Stratification, Subsets, and Covariates

The stratification factors include:

- Prior history of pancreatitis within 10 years prior to Screening (Yes vs. No)
- Previous treatment with volanesorsen (Yes vs. No)

Subgroup analysis for primary endpoint will include, but not limited to, prior history of pancreatitis within 10 years prior to Screening (Yes vs. No), previous treatment with volanesorsen (Yes vs. No), region (North America, Europe, and ROW), etc., if supported by data. Details of the subgroup analyses will be provided in the SAP.

In general, the covariate will include stratification factors and baseline measurements (where applicable), the details will be provided in Section 10.6.3.

10.2. Sample Size Considerations

Based upon prior clinical trial experience with FCS patients, the SD of the percent change from Baseline in TGs is approximately 46%. With 14 patients in each ISIS 678354 treatment group and 14 in the pooled placebo group, there would be a 90% power to detect a 60% difference between each ISIS 678354 treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the ISIS 678354 treatment patients and no change in the placebo patients. Approximately 60 patients will be enrolled in this trial to account for potential early dropouts and to facilitate some general safety evaluations.

Eligible patients will be randomized 1:1 to Cohort A or Cohort B and each cohort further randomized 2:1 (ISIS 678354:placebo) and stratified for:

- Prior history of pancreatitis within 10 years prior to Screening* vs. no history of pancreatitis or no history within 10 years prior to Screening
- Previous treatment with volanesorsen

* History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made

10.3. Analysis Populations

Full Analysis Set (FAS): All patients who are randomized and received any dose of Study Drug (ISIS 678354 or placebo). The FAS represents the practically feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9. This population will be used for the primary analysis of efficacy.

Per Protocol Set (PPS): Subset of the FAS who received at least 5 monthly doses of Study Drug within the first 6 months of the Treatment Period, and who have no major protocol violations that could compromise the interpretation of efficacy. Major violations will be determined prior to unblinding for statistical analysis. This population will be used for supportive inferences concerning efficacy.

Safety Set: All patients who are randomized and receive any dose of Study Drug. This population will be used for all safety analyses.

PK Population: All patients who are randomized and receive at least 1 dose of ISIS 678354, and have at least 1 evaluable concentration result post-first dose. This population will be used for analysis of PK data.

10.4. Definition of Baseline and Primary Time Point

For platelets, Baseline will be defined as the average of all non-missing pre-dose assessments.

Baseline for lipid measurements is defined as the average of the pre-dose measurement on Day 1 and the last measurement closest to Day 1, prior to administration of the first dose of Study Drug. The baseline for other measurements is defined as the last non-missing assessment prior to the first dose of Study Drug.

The primary analysis time point for lipid assessments is defined as the average of Weeks 23, 25, and 27 fasting assessments. If 1 or 2 of the 3 assessments are missing, then non-missing assessments will be used.

10.5. Interim Analysis and Multiplicity

No interim efficacy analysis will be performed.

To control the overall Type I error rate at 0.05 across the primary endpoints and secondary endpoints for the final analysis, the gatekeeping testing strategy will be applied to the primary endpoint family and secondary endpoint family. The hierarchical testing procedure will be utilized within the primary endpoint family and secondary endpoint family.

For the primary endpoint family, the 2 treatment arms will be compared against pooled placebo using the hierarchical testing procedure, in which the ISIS 678354 80 mg treatment group will be compared to the pooled placebo at the alpha level of 0.05, if the comparison is statistically significant ($p < 0.05$), then the ISIS 678354 50-mg treatment group is compared against the pooled placebo at the alpha level of 0.05. If the comparison of the ISIS 678354 80-mg treatment group is not statistically significant, then the comparison of the ISIS 678354 50-mg treatment group against pooled placebo and all secondary endpoints will be considered exploratory.

Testing of secondary endpoint family will be performed only if the comparison of the primary endpoint is statistically significant ($p < 0.05$) for both ISIS 678354 80-mg and 50-mg treatment groups. Testing of the secondary endpoint family will be conducted according to the following sequence:

- Secondary endpoint: comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of percent change in fasting apoC-III from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of proportion of patients who achieve $\geq 40\%$ reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting apoB-48 from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting non-HDL-C from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS

- Secondary endpoint: comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of percent change in fasting apoC-III from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting apoB-48 from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting non-HDL-C from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53/ET) between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening
- Secondary endpoint: comparison of adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53/ET) between pooled ISIS 678354 treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening
- Secondary endpoint: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS

- Secondary endpoint: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53/ET) between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Secondary endpoint: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Secondary endpoint: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS

If the comparison of the first secondary endpoint is statistically significant ($p < 0.05$), then the second secondary endpoint will be tested. However, if the comparison of the first secondary endpoint is not statistically significant, then all endpoints of lower rank will be considered exploratory. This process is repeated with each subsequent secondary endpoint.

10.6. Planned Methods of Analysis

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

The primary endpoint will be assessed on the FAS and PPS, with the former being the basis for the primary efficacy analysis. The secondary endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set.

10.6.1. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group. All patients enrolled will be included in a summary of patient disposition.

10.6.2. Safety Analysis

Treatment duration and amount of Study Drug (ISIS 678354 or placebo) received will be summarized by treatment group. Patient incidence rates of all AEs will be tabulated by MedDRA system organ class, and by MedDRA term. Tables and/or narratives of treatment emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug (ISIS 678354 or placebo) will be summarized.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count with differential, coagulation panel, etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 678354 or placebo) administration, as appropriate. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

Vital sign and ECG measures will be tabulated by treatment group.

10.6.3. Efficacy Analysis

10.6.3.1. Analysis of Primary Endpoint

The primary analysis of the primary endpoint is to compare the percent change from Baseline to the primary analysis time point in fasting TG between each ISIS 678354 treatment group vs. pooled placebo using an ANCOVA model in the FAS. The ANCOVA model will include the effects of treatment (ISIS 678354 80 mg, ISIS 678354 50 mg, or Placebo), 2 randomization stratification factors (history of pancreatitis and previous treatment with volanesorsen), and log-transformed baseline TG. To account for potential heterogeneity in variance, the 95% CI of the treatment differences will be calculated using the robust variance estimator based on the Bell and McCaffrey method (Imbens and Kolesár 2016). If patients have intercurrent event(s) before Week 23, e.g., treatment discontinuation, use of additional medication, changes in background or concomitant treatments, the Treatment Policy strategy will be implemented, the patients' assessments post intercurrent events will continue to be collected and utilized in the primary analysis. Patients with a missing TG value after discontinuation will have TG value multiply imputed at Primary analysis time point based on the known assessments from the retrieved dropouts (i.e., patients who discontinue before Week 23 but still have TG assessments at

Week 23, 25 or 27), if there is a sufficient number of retrieved dropouts. The imputation model will include the following variables: TG values at baseline and post-baseline visits and the 2 randomization stratification factors. The multiple imputation will be stratified by treatment group. If there is not a sufficient number of retrieved dropouts, missing TG value at the primary time point will be imputed using a "wash-out" (Jump to Reference, J2R) multiple imputation approach. With the approach, patients treated with ISIS 678354 who discontinue study will have missing post-discontinuation TG values multiply imputed based on the fasting TG at Baseline, 2 randomization stratification factors, and the imputation model for the placebo group. Patients in the placebo group who discontinue the study will have missing post-discontinuation TG values multiply imputed based on fasting TG values at Baseline and post-baseline visits from the placebo group.

It is anticipated that the rate of missing data is low.

The null hypothesis of the primary analysis is that the percent change from Baseline to primary analysis time point in fasting TG is the same between each ISIS 678354 and placebo treatment groups. The alternative hypothesis is that the percent change from Baseline to primary analysis time point in fasting TG is different between each ISIS 678354 and placebo treatment groups.

The primary efficacy analysis will take place after the last patient has completed the Week 53/ET visit and the database has been locked, and will be based on the percent change from Baseline in fasting TG at primary analysis time point (end of Month 6). Details of the controlled access to the unblinded data will be outlined in the SAP and Unblinding Plan.

During the database lock cleaning process, redacted source documentation may need to be shared securely with the site Clinical Research Associate (CRA) for source data verification procedures

The following sensitivity analyses of the primary endpoint will be conducted to assess the robustness of the primary analysis result, and details of the analyses will be outlined in the SAP:

- The primary analysis described above will be repeated in the PPS.
- The primary analysis will be repeated in the subset of FAS with no missing TG value at the baseline and primary analysis time point.
- Additional sensitivity analyses using controlled imputations (pattern mixture models) with ANCOVA will be conducted in the FAS to assess the robustness of the primary analysis results.
    - For patients treated with ISIS 678354 who discontinue the study due to AE or lack of efficacy (i.e., informative missing), their missing TG data after treatment discontinuation will be multiply imputed using the copy increment from reference (CIR) approach based on the estimates from of the placebo patients. The CIR approach is detailed in (Carpenter et al. 2013). The assumption is when a patient discontinues treatment due to informative missing, from withdrawal onwards he/she would progress in the same way as the patients in the placebo group. For patients who discontinue due to other reasons and all patients from the placebo group, their missing data will be treated as non-informative missing, and data will be multiply imputed based on the distribution of their own arm.

  - All patients treated with ISIS 678354 who discontinue the study will have missing post-treatment discontinuation TG values multiply imputed using the CIR approach based on the estimates from the placebo patients. Missing TG for placebo patients will be imputed based on the distribution of the placebo group.

- A nonparametric Wilcoxon rank-sum test will be performed on the percent change in fasting TG from baseline to the primary analysis time point in the FAS. Missing data will be handled using the same multiple imputation method as the primary analysis.
- An additional sensitivity analysis using the two-dimensional tipping-point approach will be conducted in the FAS to assess the impact of missing data on the result of the primary analysis. A range of penalties will be added to the imputed values for each group until the result becomes non-significant and tipping points are identified.
- An ANCOVA model will be performed in the FAS using the nature log transformed data. Missing data will be handled using the same multiple imputation method as the primary analysis.

10.6.3.2. Analysis of Secondary Endpoints

- The percent change in fasting TG from Baseline to Month 12 in the FAS will be analyzed in the same way as the primary analysis of the primary endpoint.
- The proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point in the FAS will be compared between each ISIS 678354 treatment group and placebo group using a logistic regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and log-transformed baseline TG as a covariate. Missing TG values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. A sensitivity analysis will be conducted in the FAS, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.
- The percent change in fasting apoC-III, apoB-48, and non-HDL-C from Baseline to the primary analysis time point and Month 12 in the FAS will be analyzed in the same way as the primary analysis of the primary endpoint.
- The proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point will be analyzed in the same way as the proportion of patients who achieve ≥ 40% reduction in fasting TG. Missing values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. It will be conducted in the subset of FAS with baseline TG > 880 mg/dL. A sensitivity analysis will be conducted in the subset of FAS with baseline TG > 880 mg/dL, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.
- The following adjudicated acute pancreatitis event rates
  - During the Treatment Period (Week 1 through Week 53) in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening

- During the Treatment Period (Week 1 through Week 53) in the FAS
- From Week 13 to Week 53 in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening
- From Week 13 to Week 53 in the FAS
- During the Treatment Period (Week 1 through Week 53) in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- From Week 13 to Week 53 in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment

will be compared between pooled ISIS 678354 treatment group and placebo group using a Poisson regression model or Negative Binomial regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The logarithm of time in year that each patient observed during the corresponding analysis period (Week 13 to Week 53 or Week 1 to Week 53/ET) will be used as an offset variable.

- The proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point in the FAS will be analyzed in the same way as the proportion of patients who achieve ≥ 40% reduction in fasting TG. Missing values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. A sensitivity analysis will be conducted in the FAS, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.
- The proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point will be analyzed in the same way as the proportion of patients who achieve ≥ 40% reduction in fasting TG. Missing values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. It will be conducted in the subset of FAS with baseline TG > 500 mg/dL.
  A sensitivity analysis will be conducted in the subset of FAS with baseline TG > 500 mg/dL, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

10.6.4. Pharmacokinetic and Anti-Drug Antibody Analysis

Pharmacokinetic analysis will include the following:

- Determine trough (pre-dose) and post-treatment ISIS 678354 plasma concentrations in all patients who receive Study Drug. For all patients who receive ISIS 678354 treatment, trough (pre-dose) and peak (2-hr post-treatment ISIS 678354) plasma concentrations will be summarized by treatment group, dose, day and time point, with and without stratification by ADA status, using descriptive statistics.
- For patients who receive ISIS 678354 treatment and not participating in the OLE, the plasma disposition half-life associated with the apparent terminal elimination phase will be calculated using a non-compartment method, if appropriate, using available

data. 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.

Anti-drug antibody analysis will include the following:

- Evaluate immunogenicity (IM) (confirmed positive/negative and, when applicable, titer of anti-ISIS 678354 antibodies) before, during, and after treatment with Study Drug (ISIS 678354 or placebo) in all evaluable patients and appropriately summarize by treatment and dose over time.
- Determine the IM incidence (number) and incidence rate (percent) at each evaluated study time point, and for the overall Treatment and Post-Treatment Evaluation Period and summarize by treatment and dose, as the total number of and percent of evaluated patients with antibody negative, positive, and unknown status.
- Study patients with positive anti-ISIS 678354 antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or not determinable.
- Determine subject level IM parameters, which will include but may not limited to onset and peak titer.
- Evaluate potential relationships of IM with selected efficacy, safety, and PK measures.

Additional details regarding the PK and IM analysis will be described in the SAP.

Population PK and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.5. Additional/Exploratory Analyses

The percent change in fasting TG, fasting apoC-III, fasting apoB-48, and fasting non-HDL-C from Baseline to Month 3 (average of Week 13 and Week 17), proportion of patients who achieve ≥ 40% reduction or ≥ 70% reduction in fasting TG at Month 3 and Month 12, and proportion of patients who achieve fasting TG ≤ 880 mg/dL and ≤ 500 mg/dL at Month 3 and Month 12 will also be evaluated.

The frequency and severity of patient-reported abdominal pain and other FCS-related symptoms, diet, and impacts, HRQoL, cognitive function, (Appendix E) and ER visits, incidence of all-cause hospitalizations and total inpatient days will be compared between ISIS 678354 and placebo groups.

Details of the analyses will be provided in the SAP.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or designee.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 678354 or placebo) are administered.

Importantly, patients should be informed of the possibility and risks of a reduction in platelet count and other potential risks, in particular hepatic and renal risks, and the importance of strictly adhering to the monitoring program. The patient or legally acceptable representative must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient or legally acceptable representative and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2. Ethical Conduct of the Study

The clinical trial is to be conducted in compliance with the protocol. All applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

11.3. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval.
A copy of the written approval of the protocol and informed consent form must be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study in accordance with local procedures. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4. Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator must send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

12.2. Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

12.3. Study Documentation and Storage

An eCRF utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study eCRF may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available for the duration required by GCP or local regulatory requirements, whichever is longer.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee, in accordance with GCP.

12.4. Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and "visiting" (on-site or remote access) the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., case report forms and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the case report forms. Source data should be attributable, legible,

contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved. Sponsor will ensure the Investigators are trained about the importance of patient retention, compliance with study procedures, and requirements for recording reason for missed data in the case report form. The Sponsor monitor or designee will ensure there is continuous oversight for compliance.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, the data queries, and the Study Center notifications, and agrees with the content in accordance with the general investigational plan.

12.5. Language

Case report forms must be completed in English. Whenever possible, the trade name rather than the generic name for concomitant medications should be recorded and, if possible, in English. Generic names are acceptable if the trade name is unknown. Combination medications should be recorded using their trade name in English if possible.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A Schedule of Procedures

	Screening		Treatment Period																	Follow-up Period		
	Run-in[A]	Qual																				
Study Week	-4 to -2	-2 to -1[O]	1	5[O]	9[O]	13[O]	17[O]	21[O]	23/ET -L1[O,R]	25/ET -L2[O,R]	27/ET -L3[O,R]	29[O]	33[O]	37[O]	41[O]	45[O]	49[O]	51/ET -L4[O,R]	53/ET-L5[O, R] or Tx ET[O]	4[O, P]	8[O, P]	13[O, P] / Post-Tx ET
Study Day	-28 to -15	-14 to -7	1	29	57	85	113	141	156	169	183	197	225	253	281	309	337	351	365	28[P]	56[P]	91[P]
Visit and Testing Window ± Days	0	0	-3[B]	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Informed Consent	X																					
Medical History[C]	X																					
FSH[D]	X																					
Hepatitis B, C, HIV	X																					
Genetic testing[S]	X																					
Inclusion/Exclusion Criteria	X	X																				
Body Weight and Height[E]	X		X							X									X			X
Vital Signs	X		X	X		X		X		X		X		X		X			X			X
Physical Examination	X		X			X				X				X					X			X
12-lead ECG (triplicate)	X		X			X				X				X					X			X
Pregnancy Test[F]	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X	X	X	X
Extended Urinalysis[G]	X		EVERY 14 DAYS (± 2 days)[O]				X	X		X		X	X	X	X	X	X		X	X	X	X
Serum Creatinine [H, J]	X		EVERY 14 DAYS (± 2 days)[O]				X	X		X		X	X	X	X	X	X		X	X	X	X
Chemistry Panel[I, J]	X		EVERY 14 DAYS (± 2 days)[O]				X	X		X		X	X	X	X	X	X		X	X	X	X
Hematology[J]	X	X	HEMATOLOGY PERFORMED EVERY 14 DAYS (± 2 days)[O]																			X
Coagulation (aPTT, PT, INR)	X		X							X									X			
Lipid Panel[I]	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X
HbA1c, HOMA-IR, Fructosamine, Glycated Albumin			X			X				X									X			X
hsCRP			X							X									X			X
Anti-drug Antibody			X[O, Q]		X	X				X				X					X	X	X	X
Plasma PK - ISIS 678354[K]			X[O, Q]		X	X	X	X		X		X		X		X			X	X	X	X

Appendix A Schedule of Procedures (Continued)

	Screening		Treatment Period																	Follow-up Period		
	Run-in[A]	Qual																				
Study Week	-4 to -2	-2 to -1[O]	1	5[O]	9[O]	13[O]	17[O]	21[O]	23/ET -L1[O,R]	25/ET -L2[O,R]	27/ET -L3[O,R]	29[O]	33[O]	37[O]	41[O]	45[O]	49[O]	51/ET -L4[O,R]	53/ ET-L5[O, R] or Tx ET[O]	4[O, P]	8[O, P]	13[O, P] / Post-Tx ET
Study Day	-28 to -15	-14 to -7	1	29	57	85	113	141	156	169	183	197	225	253	281	309	337	351	365	28[P]	56[P]	91[P]
Visit and Testing Window ± Days	0	0	-3[B]	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Archived Serum & Plasma Samples[I, L]			X			X			X	X	X			X		X			X			X
FCS Symptoms Two Week Recall	X																					
FCS Symptoms and Diet	DAILY DIARY																					
FCS Impacts; Pain Interference Short Form 8a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Severity (PGIS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Patient Global Impression of Change (PGIC)									X	X	X							X	X			
Health-related Quality of Life (PROMIS 29+2 Profile v2.1). PROMIS Cognitive Function 4a (optional)			X			X			X	X	X							X	X			
Assessment of ER Visits, Hospitalization and Inpatient Days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet/Alcohol Counseling[M]	X		X	X		X		X		X		X		X		X			X		X	
Study Drug: SC Injection[N]			X	X	X	X	X	X		X		X	X	X	X	X	X					

All procedures and study sample collections are to be done pre-dose at respective visits, unless specified otherwise

Legend

[A] Eligible patients will enter an approximately 4 week, but no more than 8 week, Screening Period that includes an at least 2-week Diet Stabilization/Run-In Period for patients not already on a stable diet. Patients on stable diet, for optimal control of TGs and disease management, known to the Investigator and followed at the site may go from Screening to qualification without the Diet Run-In Period

[B] Day 1/Baseline assessments can be performed up to 3 days (-3 days) prior to the actual Day 1 visit, which is the day of first Study Drug dose

[C] Patient charts will be reviewed in order to collect disease associated medical history data

Appendix A Schedule of Procedures (Continued)

[D] For confirmation of menopause at Screening per inclusion criteria

[E] Height only required at Screening

[F] Women who are not surgically sterile or post-menopausal. A serum pregnancy test will be performed during run-in and urine pregnancy tests will be performed at all other study visits, including qualification

[G] All tests listed in Appendix B under Extended Urinalysis should be performed, including routine urinalysis, urine microscopy, UACR and UPCR. Urine collection for urinalysis should not be performed during menstruation.

[H] Serum Creatinine will be collected as a part of chemistry panel

[I] Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours, unless tests are repeated for Safety reasons

[J] If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 3 days and not later than 7 days). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

[K] Refer to Appendix C for PK Sampling schedule

[L] Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report

[M] Recommended time points for qualified site personnel to reinforce compliance to diet and alcohol restrictions

[N] Cohort A: Patients to receive 50-mg Study Drug once every 4 weeks for Weeks 1-49. Cohort B: Patients to receive 80-mg Study Drug once every 4 weeks for Weeks 1-49

[O] Assessments and procedures to be conducted by either the Study Center or a Home Healthcare service (if available) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional

[P] Weeks/Days from end of treatment. End of treatment is defined as 1 dosing interval post-last dose

[Q] To be conducted on Study Days 1, 15, and 29 (each ± 2 days)

[R] Landmark visit. For early termination landmark (ET-L) visits: Week 23 is ET-L1, Week 25 is ET-L2, Week 27 is ET-L3, Week 51 is ET-L4, and Week 53 is ET-L5

[S] Redacted historical FCS genetic result reports may be collected by the Sponsor for review along with the current genetic testing

APPENDIX B. LIST OF LABORATORY ANALYTES

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 678354 or other similar oligonucleotides.

Clinical Chemistry Panel
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- ALP
- Creatine kinase
- GGT

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (for confirmation of menopause at screening per inclusion criteria)
- Serum βhCG (only women who are not surgically sterile or post-menopausal)

Coagulation
- aPTT
- PT
- INR

Lipid Panel
- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- ApoB
- ApoB-48
- Chylomicron-TG
- Triglycerides
- VLDL
- ApoC-III
- Non-HDL-C
- ApoA-1

Hematology
- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC, RDW
- Platelets
- MPV
- White blood cells (WBC)
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1]
- ISIS 678354 (total full length ASO) concentration in plasma

Immunogenicity
- Anti-ISIS 678354 antibodies

Other assessments
- HbA1c
- HOMA-IR
- Fructosamine
- Glycated albumin

Inflammatory
- hs-CRP

Extended Urinalysis
- Routine Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Blood
  - Glucose
  - Ketones
  - Bilirubin
  - Urobilinogen
  - Leukocyte esterase
  - Nitrate
- Microscopic examination
- P/C Ratio (UPCR)
- A/C Ratio (UACR)

[1] Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM or to assess other actions of ISIS 678354 with plasma constituents

APPENDIX C. PHARMACOKINETIC SAMPLING SCHEDULE

Appendix C PK Sampling Schedule

Blood samples for the determination of plasma ISIS 678354 concentrations will be collected prior to dosing, and at various time points throughout the Dosing and Post-Treatment Follow-up Period as noted in the table below. Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability and metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of ISIS 678354 with plasma constituents.

Plasma Trough and Post-Treatment Sampling Schedule for all Patients

	Treatment Period												**Follow-up Period**		
Study Week	**1**	**3**	**5**	**9**	**13**	**17**	**21**	**25/ET-L2***	**29**	**37**	**45**	**53/ET-L5* or Tx ET**	**4****	**8****	**13/Post Tx ET****
Study Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**253**	**309**	**365**	**28****	**56****	**91****
	Pre-dose, 2 hr ± 15 min***, and 4 hr ± 30 min***	Any time	Pre-dose	Pre-dose	Pre-dose and 2 hr ± 15 min	Pre-dose	Pre-dose	Pre-dose and 2 hr ± 15 min	Pre-dose	Pre-dose	Pre-dose	Any time	Any time	Any time	Any time

* Landmark visit. For early termination landmark (ET-L) visits: Week 25 is ET-L2 and Week 53 is ET-L5
** Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval post-last dose
*** Samples can be collected within the ± 15 min and ± 30 min window, but the actual sampling time should be recorded accurately in eCRF

APPENDIX D. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for AEs relating to lab test abnormalities are based upon the (CTCAE) Version 5.0, November 2017 with modifications outlined in the footnotes below.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased[1]	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased**	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs;
Children	-	Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

††Modified for consistency with ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Adapted from the original CTCAE V5.0 scale

The following grading recommendations for AEs at the injection site are based upon the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

APPENDIX E. PATIENT REPORTED OUTCOME ASSESSMENTS

Familial Chylomicronemia Syndrome (FCS) - Symptoms and Impacts

Familial Chylomicronemia Syndrome (FCS) – Symptoms (Two Week Recall)

FCS Diet Questions for Daily Diary

PROMIS® Item Bank v1.1 – Pain Interference – Short Form 8a

PROMIS® 29+2 Profile v.2.1 (PROPr)

PROMIS® Short Form v2.0 – Cognitive Function 4a

Patient Global Impression of Severity (PGIS) Scale

Patient Global Impression of Change (PGIC) Scale

Familial Chylomicronemia Syndrome (FCS)-Symptoms and Impacts

Symptoms

1. How would you rate your worst abdominal pain in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No abdominal pain										Worst possible abdominal pain

2. How would you rate your physical fatigue in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No physical fatigue										Worst possible physical fatigue

3. How would you rate your difficulty thinking in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No difficulty thinking										Worst possible difficulty thinking

4. How would you rate your diarrhea in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No diarrhea										Worst possible diarrhea

Impacts

For each of the following items, please think about how your FCS is currently affecting your life and select the response that best applies to you.

		Never	Rarely	Some-times	Often	Always
1	I worry about having a pancreatitis attack.	❑	❑	❑	❑	❑
2	I avoid making plans with other people because I don't know if I'll feel well enough.	❑	❑	❑	❑	❑
3	I feel anxious in social situations involving food.	❑	❑	❑	❑	❑
4	I avoid social situations involving food.	❑	❑	❑	❑	❑
5	I worry about eating food prepared by someone else.	❑	❑	❑	❑	❑
6	I worry about going over my dietary fat limit.	❑	❑	❑	❑	❑
7	I worry about my future health.	❑	❑	❑	❑	❑
8	I worry about being a burden to others.	❑	❑	❑	❑	❑
9	I am less physically active than I would like to be because of my FCS.	❑	❑	❑	❑	❑
10	I feel sad or depressed because of my FCS.	❑	❑	❑	❑	❑
11	I feel judged by others because of my FCS.	❑	❑	❑	❑	❑
12	I worry about my finances because of my FCS.	❑	❑	❑	❑	❑
13	I am less productive than I would like to be (at work, home, and/or school) because of my FCS.	❑	❑	❑	❑	❑

Familial Chylomicronemia Syndrome (FCS)- Symptoms (Two week Recall)

Symptoms

1. How would you rate your worst abdominal pain in the past 2 weeks?

	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
	No abdominal pain										Worst possible abdominal pain

2. How would you rate your physical fatigue in the past 2 weeks?

	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
	No physical fatigue										Worst possible physical fatigue

3. How would you rate your difficulty thinking in the past 2 weeks?

	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
	No difficulty thinking										Worst possible difficulty thinking

4. How would you rate your diarrhea in the past 2 weeks?

	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
	No diarrhea										Worst possible diarrhea

FCS Diet Questions for Daily Diary

Did you fast (not eat) in the past 24 hours? *(select one)*

- o I completely fasted and did not eat
- o I partially fasted and ate less than I normally would
- o I did not fast and ate as I normally do

If endorse item 2 or 3, follow up with:

How would you describe your dietary fat intake in the past 24 hours? *(select one)*

- o I have eaten less than 10g of fat
- o I have eaten 10 – 20g of fat
- o I have eaten more than 20g of fat

PROMIS® Item Bank v1.1 – Pain Interference – Short Form 8a

Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ12	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ36	How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ3	How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ13	How much did pain interfere with your family life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS® 29+2 Profile v2.1 (PROPr)

Please respond to each question or statement by marking one box per row.

	Physical Function	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS® 29+2 Profile v2.1 (PROPr)

	Fatigue In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS® 29+2 Profile v2.1 (PROPr)

	Pain Interference In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Cognitive Function - Abilities In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PC6r	I have been able to concentrate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC27r	I have been able to remember to do things, like take medicine or buy something I needed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Pain Intensity In the past 7 days…											
Global07	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

PROMIS® Item Bank v2.0 – Cognitive Function- Short Form 4a

Cognitive Function- Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	**Never**	**Rarely (Once)**	**Sometimes (Two or three times)**	**Often (About once a day)**	**Very often (Several times a day)**
PC2r	My thinking has been slow.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC35r	It has seemed like my brain was not working as well as usual.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC36r	I have had to work harder than usual to keep track of what I was doing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC42r	I have had trouble shifting back and forth between different activities that require thinking	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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Patient Global Impression of Severity (PGIS) Scale:

Please choose the response below that best describes the severity of your Familial Chylomicronemia Syndrome over the past week. *(Select one)*

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very severe

Patient Global Impression of Change (PGIC) Scale:

Please choose the response below that best describes the overall change in your Familial Chylomicronemia Syndrome since you started taking the study medication. *(Select one)*

- □ Much better
- □ A little better
- □ No change
- □ A little worse
- □ Much worse

Protocol

Version:	1
Version Date:	04 Aug 2023
Title:	678354-CS3 Protocol Amendment 9: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRx (ISIS 678354) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

APPROVALS:

[redacted] Clinical Development [redacted] [redacted] 04-Aug-2023 21:57:55 GMT+0000

Parexel International

IONIS PHARMACEUTICALS, INC.

Protocol Number: ISIS 678354-CS3 (AKCEA-APOCIII-LRx)

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRX Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Statistical Analysis Plan

Version: 4.0

Parexel Project Number: 243920

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Approved by:

See electronic signature and date attached at end of document

[redacted] Biometrics
Ionis Pharmaceuticals, Inc.

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Ionis Pharmaceuticals, Inc.

Parexel SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

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

	Signatory
Author	[redacted] Project Role: Biostatistics[redacted]

TABLE OF CONTENTS

REVISION HISTORY

The following table lists the major modifications to ISIS 678354-CS3 Statistical Analysis Plan (SAP) Version 3.0, dated 6 Jun 2023. Minor changes have also been made throughout the document to improve the overall clarity of the original SAP and consistency across the sections

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
2.2	Secondary Objectives	List of secondary objectives updated – new **added**, order changed**:** o Percent change in fasting apoC-III from Baseline o Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline o ~~Proportion of patients who achieve fasting TG ≤ 750 mg/dL (8.4 mmol/L)~~ o Percent change in fasting apoB-48 from Baseline o Percent change in fasting non-HDL-C from Baseline o **Adjudicated acute pancreatitis event rate in patients with a prior history of pancreatitis within 10 years prior to Screening** o ~~Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment~~ o Adjudicated acute pancreatitis event rate o Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline o **Proportion of patients who achieve fasting TG ≤880 mg/dL (10 mmol/L)** o **Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment** o Proportion of patients who achieve fasting TG ≤ 500 mg/dL (5.7 mmol/L)

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
3.2.2	Secondary Endpoint	List of secondary endpoints updated – new **added**, order changed**:** o Percent change in fasting TG from Baseline at 12 months (average of Weeks 51 and 53) compared to placebo o Percent change in fasting apoC-III from Baseline at the primary analysis time point compared to placebo o Percent change in fasting apoC-III from Baseline at 12 months compared to placebo o Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline at the primary analysis time point compared to placebo ~~o Proportion of patients who achieve fasting TG ≤ 750 mg/dL at the primary analysis time point compared to placebo~~ o Percent change in fasting apoB-48 from Baseline at the primary analysis time point compared to placebo o Percent change in fasting non-HDL-C from Baseline at the primary analysis time point compared to placebo o **Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with a prior history of pancreatitis within 10 years prior to Screening** ~~o Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment~~ o Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo o **Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with a prior history of pancreatitis within 10 years prior to Screening** ~~o Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment~~ o Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo o Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline at the primary analysis time point compared to placebo o Percent change in fasting non-HDL-C from Baseline at 12 months compared to placebo o Percent change in fasting apoB-48 from Baseline at 12 months compared to placebo o **Proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point compared to placebo** o **Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment** o **Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment** o Proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point compared to placebo

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.5	Analysis Sets	Definition of PPS updated: Per Protocol Set (PPS): Subset of the FAS who received at least 5 monthly doses of Study Drug within the first 6 months (172 days) of the Treatment Period, ~~have a baseline TG assessment~~ and who have no significant protocol violations that could compromise the interpretation of efficacy
4.9.1.2	Handling of Dropouts or Missing Data	Section updated: If there is no sufficient number of retrieved dropouts, missing TG value at the primary analysis time point will be imputed using a "wash-out" multiple imputation approach (Jump to Reference, J2R). With the approach, patients treated with ISIS 678354 ~~who discontinue study~~ will have missing ~~post discontinuation~~ TG values **after the last dosing date** multiply imputed based on baseline fasting TG, the 2 stratification factors of their own treatment group, and the imputation model for the placebo group. Patients in the placebo group ~~who discontinue the study~~ will have missing ~~post discontinuation~~ TG values multiply imputed based on baseline fasting TG, fasting TG values at post-baseline visits and the 2 stratification factors from the placebo group. **The "wash-out" multiple imputation will be preformed in the following steps:** **1.** The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute ~~the~~ **all** missing values by treatment group. The variable list for imputations will include the baseline value, as well as all available post-baseline value, and stratification factors. To conform to the multivariate normality assumption, baseline, and post-baseline fasting lipid data will be natural log-transformed before the imputation process, and the variable values will be back transformed to create the imputed data set. The SAS procedure PROC MI will be used in the multiple imputation. The MCMC method will impute **primary analysis time point data** ~~one dataset for~~**for**~~rom~~ each **of the 100**~~imputed~~ dataset**s** from the first imputation stage. EM algorithm will be used to derive a set of initial parameter estimates for MCMC method. A non-informative prior (Jeffreys' prior) will be used to derive the posterior distribution of the parameters. A **total of** 100 imputed datasets will be created from the above 2-stage multiple imputation process…… **2. A general linear model will be fitted using the data in the placebo group for each imputed dataset** 3. **For patients in both ISIS 678354 dose groups, the imputed values after last dose date will be replaced with the values imputed using J2R method (calculated using the patients' own baseline fasting TG, the 2 stratification factors, and the model from step 2)** 4. **The variable values will be back transformed from nature log scale to the original scale in the final imputed datasets.**

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.9.1.3	Multiplicity	New secondary endpoints **added and testing sequence is updated:** o Secondary endpoint 1: comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS o Secondary endpoint 2: comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS o Secondary endpoint 3: comparison of percent change in fasting apoC-III from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS o Secondary endpoint 4: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 80 mg treatment group and pooled placebo in FAS ~~o Secondary endpoint 5: comparison of proportion of patients who achieve fasting TG ≤ 750 mg/dL at the primary analysis time point between ISIS 678354 80 mg treatment group and pooled placebo in FAS~~ o Secondary endpoint **5**: comparison of percent change in fasting apoB-48 from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS o Secondary endpoint **6**: comparison of percent change in fasting non-HDL-C from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS o Secondary endpoint **7**: comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS o Secondary endpoint **8**: comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS o Secondary endpoint **9**: comparison of percent change in fasting apoC-III from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS o Secondary endpoint **10**: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS ~~o Secondary endpoint 12: comparison of proportion of patients who achieve fasting TG ≤ 750 mg/dL at the primary analysis time point between ISIS 678354 50 mg treatment group and pooled placebo in FAS~~ o Secondary endpoint **11**: comparison of percent change in fasting apoB-48 from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS o Secondary endpoint **12**: comparison of percent change in fasting non-HDL-C from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS o **Secondary endpoint 13: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening**

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.9.1.3	Multiplicity(Continued)	○ Secondary endpoint **14**: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in FAS ○ **Secondary endpoint 15: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening** ○ Secondary endpoint **16**: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the FAS ○ Secondary endpoint **17**: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS ○ Secondary endpoint **18**: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS ○ Secondary endpoint **19**: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS ○ **Secondary endpoint 20: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS** ○ Secondary endpoint **21**: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS ○ Secondary endpoint **22**: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS ○ Secondary endpoint **23**: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS ○ **Secondary endpoint 24: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS** ○ Secondary endpoint 25: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment ○ Secondary endpoint 26: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.9.1.3	Multiplicity(Continued)	○ Secondary endpoint 27: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS ○ Secondary endpoint 28: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
4.9.2.	Primary Efficacy Variable	Section updated: 1) Patients with missing TG value at the primary analysis time point will be imputed using a pattern mixture model. Specifically, for patients treated with ISIS 678354 who discontinue the ~~study~~ **treatment** due to AE or lack of efficacy (i.e., informative missing), their missing fasting TG data after ~~treatment discontinuation~~ **the last dosing date** will be multiply imputed using the copy increment from reference (CIR) approach based on the estimates from of the placebo patients. The CIR approach is detailed in (Carpenter *et al.* 2013). The assumption is when a patient discontinues treatment due to informative missing, from withdrawal onwards he/she would progress in the same way as the patients in the placebo group. For patients who discontinue due to other reasons and all patients from the placebo group, their missing data will be treated as non-informative missing, and data will be multiply imputed based on the distribution of their own treatment group. 2) All patients treated with ISIS 678354 ~~who discontinue the study~~ will have missing ~~post treatment discontinuation~~ TG values **after the last dosing date** multiply using the CIR approach based on the estimates from the placebo patients. Missing TG values for placebo patients will be imputed based on the distribution of the placebo group.
4.9.3.2.	Proportion of Patients who Achieve ≥ 40% Reduction in Fasting TG from Baseline at the Primary Analysis Time Point	Section updated: Sensitivity Analysis 1: An additional analysis will be conducted in the FAS, in which all patients who have missing data and discontinue ~~study~~ **treatment** before Week 23 will be considered as non-responders.
4.9.3.4	Proportion of Patients who Achieve Fasting TG ≤ 880 mg/dL at Primary Analysis Time Point	• TG reduction level changed to 880: ○ The proportion of patients who achieve fasting TG ≤ ~~750~~ **880** mg/dL

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.9.3.5	Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 in the Subset of FAS with a prior history of pancreatitis within 10 years prior to Screening	Section changed to: ○ Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 in the Subset of FAS with **a prior history of pancreatitis within 10 years prior to Screening** ~~≥ 2 Events of Adjudicated Acute Pancreatitis in 5 years Prior to Enrollment~~ Description added: ○ The adjudicated acute pancreatitis event rate from Week 1 to Week 53 in the subset of FAS with **a prior history of pancreatitis within 10 years prior to Screening**~~≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment~~ will be compared between pooled ISIS 678354 treatment and placebo group using a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment**, i.e., events occurred within 1826 days (calculated by 365.25 times 5 and rounded to integer) before the first dose date and up to the first dose date and time,** as a covariate.
4.9.3.7	Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 in the Subset of FAS with a prior history of pancreatitis within 10 years prior to Screening	• Section changed to: ○ Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 in the Subset of FAS with **a prior history of pancreatitis within 10 years prior to Screening** ~~≥ 2 Events of Adjudicated Acute Pancreatitis in 5 years Prior to Enrollment~~
4.9.3.9.	Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 in the Subset of FAS with ≥ 2 Events of Adjudicated Acute Pancreatitis in 5 years Prior to Enrollment	• Section added
4.9.3.10	Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 in the Subset of FAS with ≥ 2 Events of Adjudicated Acute Pancreatitis in 5 years Prior to Enrollment	• Section added
4.9.3.12.	Proportion of atients who Achieve Fasting TG ≤ 500 mg/dL at Primary Analysis Time Point	Baseline fasting TG level changed to 500 mg/dL: with baseline fating TG > ~~750~~ **500** mg/dL.
4.10.	Safety Evaluation	Analyses added: **Risk difference and corresponding 95% CI in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group in selected safety endpoint will be provided. The crude incidence rate (or percentage) is defined as the number of patients who experienced at least one event times 100 divided by the total number of patients. The 95% CI of risk difference in crude incidence rate will be estimated using the Miettinen-Nurminen (MN) method.**

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.10.1	Extent of Exposure	Added analysis: ○ **A summary of number of days of dose interruption.**
4.10.3.	Adverse Events of Special Interest	Added analyses: **The number and percentage of patients experiencing events as well as the total number of reported events, classified by SOC and PT, will be tabulated by treatment group.** **The following additional analyses may be provided if supported by data:** ○ **A cumulative incidence plot** ○ **Risk difference and its 95% CI in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group. The analysis methods are detailed in Section 4.10 of this SAP.** ○ **Exposure adjusted incidence rates (EAIRs) and risk difference (or ratio) in EAIRs may also be provided, if deemed necessary. EAIR is defined as the number of patients who experienced at least one event times 100 divided by total patient-years at risk for the event. For patients with events, the time at risk is the time from the first dose date to the first onset of an event (i.e., first event date minus first dose date plus one day divided by 365.25); for patients with no event, the time at risk is the total duration in the on-study period (i.e., last participation date minus first dose date plus one day divided by 365.25).** ○ **Exposure adjusted event rates (EAERs), defined as the number of events times 100 divided by the total duration in the on-study period in year.**
4.10.4.1.	Local Cutaneous Reactions at the Injection Site	Added analysis: In addition, for patients who experienced LCRIS, **time to onset of the first event**, the number of injections prior to the first LCRIS will also be summarized descriptively by treatment group and total ISIS 678354 treated.
4.10.4.2	Injection Site Reaction	Added analysis: In addition, for patients who experienced ISR, **time to onset of the first event**, the number of injections prior to the first ISR will also be summarized descriptively by treatment group and total ISIS 678354 treated.
4.10.4.3	Flu-like Reactions	Section updated: Flu-like reactions **(FLR) will be evaluated using the following 2 definitions**: **Definition 1 (FLR 1): defined as adverse events with PTs including Influenza like illness, Pyrexia, Feeling hot, Body temperature increased, Chills, Myalgia, or Arthralgia, starting on the day of injection or next day.** **Definition 2 (FLR 2): defined as** ~~are defined as~~ adverse events with PTs including either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, plus at least two of the following symptoms with the PTs: Chills, Myalgia, or Arthralgia, starting on day of injection or the next day. ….. **For the subset of patients experiencing FLR(s), the time to onset of first FLR will be summarized using descriptive statistics**.

Section	Section Title	Description of Changes (Additions in bold. Deletions in strikethrough)
4.10.4.4.	Bleeding TEAE	Section updated: **Bleeding TEAEs will be analyzed for the following categories. The number and percentage of patients experiencing events as well as the number of reported events, classified by SOC and PT, will be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided.** ○ **Bleeding TEAEs (defined based on the 'Haemorrhages' Standardized MedDRA Query [SMQ, both narrow and broad scope])** ○ **Clinical bleeding TEAEs, i.e. bleeding TEAEs excluding events at the injection site and events related to a laboratory value** ○ **Clinical bleeding events with concomitant anticoagulant or antiplatelet medication** ○ **Clinical bleeding events without concomitant anticoagulant or antiplatelet medication** ~~Bleeding AEs will be identified based on the Haemorrhages (SMQ) Export from MedDRA and summarized by MedDRA system organ class and preferred term and by treatment group.~~ ~~Bleeding AEs excluding bleeding at the injection will be summarized by MedDRA system organ class and preferred term and by treatment group.~~
4.10.4.5.	Thrombocytopenia TEAE	• Section added
4.10.4.6	Hypersensitivity TEAE	• Section added
4.10.4.7	Renal Impairment TEAE	• Section added
4.10.4.8.	Abnormal Liver Function TEAE	• Section added
4.10.5.	Clinical Laboratory Evaluation	Categories for abnormality levels updated.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
apo	apolipoprotein
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CIR	increment from reference
CRF	case report form
CRO	contract research organization
CTR	clinical trial report
CV	coefficient of variation
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DRM	data review meeting
DSMB	data and safety monitoring board
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
EAER	exposure adjusted event rate
eDISH	evaluation of Drug Induced Serious Hepatoxicity
eGFR	estimated glomerular filtration rate
EOS	end-of-study
ER	emergency room
ET	early termination
FLRs	flu-like reactions
FCS	familial chylomicronemia syndrome
FMQ	FDA medical query
GFR	glomerular filtration rate
HbA1c	glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HRQoL	health-related quality of life
IB	investigator's brochure
ICF	informed consent form
IEC	independent ethics committee
IM	immunogenicity
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
LDL	low-density lipoprotein

Abbreviation / Acronym	Definition / Expansion
MACE	major adverse cardiovascular events
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
MN	Miettinen-Nurminen
MNAR	missing not at random
NA	not available
OLE	open-label extension
PD	protocol deviation
PK	pharmacokinetic
PMM	pattern mixture model
PPS	per-protocol set
PT	preferred term
ROW	rest of world
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	system organ class
TEAE	treatment-emergent adverse event
TG	triglycerides
UACR	urinary albumin/creatinine ratio
ULN	upper limit of normal
UPCR	urinary protein/creatinine ratio
VLDL	very low-density lipoprotein
WBCs	white blood cells
WHO-DD	world health organization - drug dictionary

1. INTRODUCTION

The analyses described in this SAP are based upon the following Ionis study documents:

- Study Protocol, Amendment 7 – ROW (October 26, 2022)
- Study Protocol, Amendment 8 – UK (February 23, 2023)
- Study Protocol, Amendment 6 – Germany (December 7, 2021)
- Study Protocol, Amendment 9 – France (October 17, 2022)
- Study Protocol, Amendment 9 –ROW (August 2, 2023)

This SAP details the procedures for the pharmacokinetic (PK), efficacy and safety statistical methods used to analyze the data.

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

Revision of this SAP will not be required for any subsequent amendments to the protocol which do not change the analyses described in this SAP. Revisions to specifics such as blood sample collection times, etc. will not require an update to the SAP.

2. STUDY OBJECTIVES

2.1. Primary Objective

To evaluate the efficacy of ISIS 678354 (olezarsen) as compared to placebo on the percent change in fasting triglycerides (TG) from Baseline

2.2. Secondary Objectives

To evaluate the efficacy of ISIS 678354 as compared to placebo on the following:

- Percent change in fasting apoC-III from Baseline
- Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline
- Percent change in fasting apoB-48 from Baseline
- Percent change in fasting non-HDL-C from Baseline
- Adjudicated acute pancreatitis event rate in patients with a prior history of pancreatitis within 10 years prior to Screening
- Adjudicated acute pancreatitis event rate
- Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline
- Proportion of patients who achieve fasting TG ≤ 880 mg/dL (10 mmol/L)
- Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Proportion of patients who achieve fasting TG ≤ 500 mg/dL (5.7 mmol/L)

2.3. Additional/Exploratory Objective(s)

To evaluate the effect of ISIS 678354 as compared to placebo on:

- Patient-reported abdominal pain, other FCS-related symptoms (physical fatigue, difficulty thinking and diarrhea), diet, and impacts, and health-related quality of life (HRQoL), pain interference and cognitive function.
- Emergency room (ER) visits, incidence of all-cause hospitalizations and total inpatient days

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a multi-center, randomized, double-blind, placebo-controlled study. Eligible patients will enter an approximately 4-week, but no more than 8-week, Screening Period that includes an at least 2-week Diet Stabilization/Run-In Period for patients not already on a stable diet, and an approximately 2-week Qualification Period. Following qualification, approximately 60 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 2:1 to receive ISIS 678354 or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of ISIS 678354 once every 4 weeks or matching volume of placebo (0.5 mL) Weeks 1-49, of the Treatment Period. Patients in Cohort B will receive 80 mg ISIS 678354 once every 4 weeks or matching volume of placebo (0.8 mL) Weeks 1-49 of the Treatment Period. Randomization will be stratified by (1) prior history of pancreatitis (within 10 years prior to Screening) and (2) previous treatment with volanesorsen. 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. Following the Week 53 visit, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the institutional review board/independent ethics committee (IRB/IEC) and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post Treatment Evaluation Period. The primary endpoint for the study will be evaluated after the last patient has completed the Week 53/ET visit and will be based on the percent change in fasting TG from Baseline at the primary analysis time point (Month 6).

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

- A screening period of up to 8 weeks is given to complete the screening and baseline assessments. An approximately 4-week but no more than 8-week Screening Period including a Diet Stabilization Period of at least 2 weeks and an approximately 2-week Qualification Period (patients on stable diet, for optimal control of TGs and disease management, known to the Investigator and followed at the site may go from Screening to Qualification without the Diet Run-In Period)
- The Treatment Period is 53 weeks. Eligible patients will have assessments at specified intervals throughout the 53-week Treatment Period. During the Treatment Period, Study Drug is administered by SC injection once every 4 weeks (Week 1 through Week 49).

- The Post-Treatment Follow-up Period is 13 weeks with assessments. Alternatively, following the Week 53 visit, eligible patients may elect to enroll in an OLE study pending study approval of this proposed study by the IRB/IEC and the appropriate regulatory authority.

The End-of-Study is defined as last patient, last visit. For individual patients, End-of-Study is defined as completion of their last study visit.

3.2. Endpoints

The primary analysis time point is at the end of Month 6 where the value is defined as the average of Weeks 23, 25 and 27 assessments.

3.2.1. Primary Endpoints

The primary endpoint is the percent change in fasting TG from Baseline at the primary analysis time point compared to placebo.

3.2.2. Secondary Endpoints

The secondary endpoints include the following:

- Percent change in fasting TG from Baseline at 12 months (average of Weeks 51 and 53) compared to placebo
- Percent change in fasting apoC-III from Baseline at the primary analysis time point compared to placebo
- Percent change in fasting apoC-III from Baseline at 12 months compared to placebo
- Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline at the primary analysis time point compared to placebo
- Percent change in fasting apoB-48 from Baseline at the primary analysis time point compared to placebo
- Percent change in fasting non-HDL-C from Baseline at the primary analysis time point compared to placebo
- Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with a prior history of pancreatitis within 10 years prior to Screening
- Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo
- Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with a prior history of pancreatitis within 10 years prior to Screening
- Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo
- Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline at the primary analysis time point compared to placebo
- Percent change in fasting non-HDL-C from Baseline at 12 months compared to placebo
- Percent change in fasting apoB-48 from Baseline at 12 months compared to placebo
- Proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point compared to placebo

- Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point compared to placebo

3.2.3. Additional/Exploratory Endpoints

To evaluate the effect of ISIS 678354 as compared to placebo on:

- Patient-reported abdominal pain, other FCS-related symptoms (physical fatigue, difficulty thinking and diarrhea), diet, and impacts, HRQoL, pain interference and cognitive function.
- ER visits, incidence of all-cause hospitalizations and total inpatient days

3.2.4. Safety Variables

Safety and tolerability assessments include adverse events, clinical laboratory tests, electrocardiogram (ECGs), use of concomitant medications, and independently adjudicated event rates of Major Adverse Cardiovascular Events (MACE) for ISIS 678354 as compared to placebo.

4. STATISTICAL METHODS

4.1. Data Management and Quality Assurance

4.1.1. Central Laboratory Data

Ionis Pharmaceuticals, Inc. (Ionis) and Medpace are responsible for the format of the laboratory electronic data transfers and the transfer schedule. Central laboratory data results are not stored in the EDC system. Medpace and Ionis are responsible for the review of the clinical laboratory data. This process involves reviewing the patient and visit identifiers in the central laboratory data results data against the central lab data identifiers collected in the EDC system. Investigator sites have access to the data via lab reports sent directly from the laboratory or through the laboratory's web portal (in which case Investigators only have access to data from their site).

The Sponsor, Investigator and patients will be kept blinded to post-baseline laboratory lipid panel results (TG, apoC-III, total cholesterol, LDL cholesterol, HDL cholesterol, apoB, apoB-48, chylomicron-TG, VLDL, non-HDL-C, and apoA-1) which can jeopardize the blinding of treatment allocation, alter Investigator's clinical practice, or are part of study endpoints to avoid bias in the conduct of the study. Beginning at Week 27, if a patient has an LDL-C > 130 mg/dL (> 100 mg/dL for patients with T2DM or CAD with Baseline LDL-C > 100 mg/dL) on 2 consecutive visits, the LDL-C values for this patient will be unblinded for the remainder of the study.

4.1.2. Pharmacokinetic Data

Ionis 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. Prior to unblinding of the final analysis, any PK concentration datasets provided to Ionis by the bioanalytical lab will be provided without reference to actual patient

identifiers to avoid inadvertent or accidental unblinding. The bioanalytical lab may provide Ionis with datasets containing dummy patient identifiers unrelated to the actual identifiers to allow review of the PK data.

4.1.3. Adjudicated Data

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) as outlined in the Pancreatitis Adjudication Charter. In addition, data for episodes of acute pancreatitis or suspected pancreatitis in the 5 years prior to enrollment will be collected by review of each patient's medical chart and these events will also be adjudicated.

All AEs and SAEs that occur during the study that are consistent with a MACE will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

4.1.4. Patient Reported Outcome Assessments

The patient reported outcome assessments will be captured by YPrime eCOA System. Patients will enter their assessments into the system using a study-dedicated tablet and handheld devices. Ionis and YPrime are responsible for the format of the electronic data transfers and the transfer schedule. The patient reported outcome assessments will not be stored in the EDC system. Ionis and YPrime are also responsible for the review of the data. This process involves reviewing the patient and visit identifiers in the assessment data against the data identifiers collected in the EDC system. The YPrime system for data collection includes built-in measures to prevent missing items for any completed questionnaire.

4.1.5. Other Data

Genetic lab data will be provided by PreventionGenetics. Platelet antibody data will be provided by Versiti Wisconsin, Inc. Platelet and Immunology Reference Lab. Ionis, PreventionGenetics and Versiti Wisconsin are responsible for the review of the data, the format of the electronic data transfers and the transfer schedule. These data will also not be stored in the EDC system but will be transferred to Ionis as external data.

4.2. General Considerations

4.2.1. Data Presentation

Descriptive summary statistics including n, mean, median, standard error, standard deviation, interquartile range (25^{th} percentile, 75^{th} percentile), range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

All statistical tests will be conducted using 2-sided tests with 5% Type 1 error rates unless otherwise stated. P-values greater than or equal to 0.0001, in general, will be presented to four decimal places. P-values less than 0.0001 will be presented as "< 0.0001".

Confidence intervals will be presented to one more decimal place than the raw data.

Any outliers that are detected during the review of the data before database lock will be investigated. If necessary, queries will be issued to the Investigator, to either correct or confirm the outlier.

The primary endpoint will be assessed on the Full Analysis Set (FAS) and Per Protocol Set (PPS), with the former being the basis for the primary efficacy analysis. The secondary endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set (SS). PK endpoints will be assessed in the PK Set as applicable.

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

All tables and figures containing efficacy endpoints will indicate whether they present raw data or adjusted results from the statistical model, with footnotes indicating the model used and covariates included in the model.

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel (a CRO that is responsible for pre-programming datasets and TLFs for the Study) procedures.

Missing visits or missing data related to COVID-19 may be provided in the data lstings if supported by data. Additional listings may be provided for all patients impacted by COVID-19 during conduct of the study and additional summary (s) and/or analyses may be provided if deemed necessary.

4.2.2. Baseline Consideration

Baseline for lipid measurements is defined as the average of the pre-dose measurement on Day 1 and the last measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug. If 1 of the 2 measurements is missing, then the other measurement will be assigned as the baseline value. If all pre-dose measurements are missing, then the baseline will be set as missing. Missing baseline values will be imputed using the multiple imputation method described in Section 4.9.1.2 in the SAP. Note that if on Day 1, there are multiple pre-dose assessments, then the last assessment with non-missing value will be used as the Day 1 pre-dose assessment.

Baseline consideration for exploratory endpoints:

1. Average worst FCS Symptoms (abdominal pain, physical fatigue, difficulty thinking, diarrhea, and composite symptom score): baseline is defined as the average during the screening period and up to Day 1; an alternative baseline is defined as single observation collected at the first day of screening with a two-week recall.
2. Highest worst FCS Symptoms: baseline is defined as the highest (worst) score during the screening period and up to Day 1.
3. FCS Impacts, PROMIS pain interference, HR-QoL (PROMIS 29+2 Profile v2.1), PROMIS cognitive function, and Patient Global Impression of Severity (PGIS): baseline is defined as the last non-missing assessment on or prior to Day 1

The ECG measurements will be performed in triplicate at each visit. Baseline for continues variables is defined as the average of the last non-missing triplicate prior to the first dose of Study Drug.; Baseline for categorical variable is defined as the worst of the last non-missing triplicate prior to the first dose of Study Drug. If only one or two measurements are available, the baseline will be determined from the available measurements.

The baseline for platelet is defined as the average of all assessments prior to the first dose of Study Drug.

The baseline for other measurements is defined as the last non-missing assessment prior to the first dose of Study Drug.

4.2.3. Primary Analysis Time Point, Months 3 and 12, and Treatment Period

The primary analysis time point is defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments are missing, then non-missing assessments will be used. Month 3 is defined as the average of Weeks 13 and 17. Month 12 is defined as the average of Weeks 51 and 53. For Month 3 or Month 12, if 1 assessment is missing, then non-missing assessment will be used.

The treatment period is defined as the time period from the first dose administration to the earliest date from 42 days after the last dose of Study Drug and last contact date within the study.

4.2.4. Visit Windows

The efficacy and exploratory measures will be mapped to analysis visits according to the visit windows in the table below.

The intent of these visit windows is not to align with those prescribed for visit scheduling in the 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. Visits after Week 53 are part of the post-treatment assessment period and, due to the fact that most patients are expected to roll into the OLE study, these data will only be provided in patient listings for evaluation of individual patient safety rather than being tabulated. Therefore, no visit windows are needed for data analysis for these visits. If a patient discontinued early from the treatment period but attended applicable landmark visits to collect efficacy assessments, then those assessments should be mapped to analysis visits and utilized in the analyses as well, unless otherwise stated.

For Daily FCS Symptoms questionnaire using average, data in the same visit window will be averaged.

For Daily FCS Symptoms questionnaire using the highest (worst) score, the highest score in each visit window will be determined.

For other data, if there are multiple assessments within a visit window, the assessment nearest the target day will be used unless two assessments are equally near, in which case the average value will be used. For 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	Nominal Visit (Target Day)	Analysis Visit Window (Day)
Lipid Panel	Week 5 (Day 29)	2-43
	Week 9 (Day 57)	44-71
	Week 13 (Day 85)	72-99
	Week 17 (Day 113)	100-127
	Week 21 (Day141)	128-148
	Week 23 (Day 156)	149-162
	Week 25 (Day 169)	163-176
	Week 27 (Day 183)	177-190
	Week 29 (Day 197)	191-225
	Week 37 (Day 253)	226-281
	Week 45 (Day 309)	282-330
	Week 51 (Day 351)	331-358
	Week 53 (Day 365)	359-379[a]
Daily FCS Symptoms	Week 2 (Day 8)	2-8
	Week 3 (Day 15) – Week 53 (Day 365)	(Week-1)*7-5 to (Week-1)*7+1
FCS Impacts; Pain Interference & PGIS	Week 5 (Day 29)	2-43
	Week 9 (Day 57)	44-71
	Week 13 (Day 85)	72-99
	Week 17 (Day 113)	100-127
	Week 21 (Day141)	128-148
	Week 23 (Day 156)	149-162
	Week 25 (Day 169)	163-176
	Week 27 (Day 183)	177-190
	Week 29 (Day 197)	191-211
	Week 33 (Day 225)	212-239
	Week 37 (Day 253)	240-267
	Week 41 (Day 281)	268-295
	Week 45 (Day 309)	296-323
	Week 49 (Day 337)	324-344
	Week 51 (Day 351)	345-358
	Week 53 (Day 365)	359-379 [a]
PGIC	Week 23 (Day 156)	149-162
	Week 25 (Day 169)	163-176
	Week 27 (Day 183)	177-190
	Week 51 (Day 351)	331-358
	Week 53 (Day 365)	359-379 [a]
Health-related QOL (PROMIS 29+2 Profile v2.1) & PROMIS Cognitive Function	Week 13 (Day 85)	72-99
	Week 23 (Day 156)	149-162
	Week 25 (Day 169)	163-176
	Week 27 (Day 183)	177-190
	Week 51 (Day 351)	331-358
	Week 53 (Day 365)	359-379 [a]

[a] 379 represents the middle point between the target days for the Week 53 visit and the first post-treatment assessment visit.

All other 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 from the central lab will not be included in the by-visit summaries but will be used in the determination of baseline, laboratory abnormality summaries and shift analyses, and presented in data listings. Local lab data will be only used in platelet analyses (including by visit summary, abnormality summaries, and shift from Baseline to worst post-baseline), and presented in data listings. For other safety lab parameters, local lab data will not be included in any analyses and data summaries.

4.3. Software

All report outputs will be produced using SAS® Version 9.4 or a later version in a secure and validated environment.

4.4. Study Subjects

4.4.1. Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- A summary of the number and percentage of subjects who were screened, randomized, and subjects who are excluded prior to randomization by major reason and overall, using the all screening patients.
- A summary of the number and percentage of patients treated (with at least one dose or partial dose of IMP) and terminating from treatment, and the number and percentage of major reason of patient terminating from treatment by treatment group, total ISIS 678354-treated (50 mg +80 mg) and overall.
- A summary of the number and percentage of patients completed the study and terminating from the study, and the number and percentage of major reason of patient terminating from the study, by treatment group, total ISIS 678354-treated (50 mg + 80 mg) and overall.
- The percentage of patients treated, the percentage of patients who discontinued from treatment and the percentage of patients who discontinued from study will be calculated based on the number of patients randomized.

A by-subject listing of disposition data will be provided based on the randomized subjects. Listing of eligibility criteria will be provided. A separate disposition listing for screen failures will also be provided.

4.4.2. Protocol Deviations

Protocol Deviations (PDs) will be classified as “major” or “minor” based on study protocol deviation guidance. All protocol deviations and major protocol deviations will be summarized by deviation category. The PD summaries will include the number and percentage of subjects with a PD by treatment group and overall, and by type of deviation, based on the randomized subjects. All protocol deviations will be listed.

Significant protocol deviations are defined as those deviations from the protocol likely to impact the perceived efficacy and/or safety of study treatments. The impact of significant protocol deviations on

the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by significant protocol deviations. Before unblinding, the data will be reviewed by the clinical group for identification of significant protocol deviations.

4.5. Analysis Sets

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 randomized and received any amount of Study Drug (ISIS 678354 or placebo). The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9. This population will be used for the primary analysis of efficacy.

Per Protocol Set (PPS): Subset of the FAS who received at least 5 monthly doses of Study Drug within the first 6 months (172 days) of the Treatment Period, and who have no significant protocol violations that could compromise the interpretation of efficacy. Significant violations will be determined prior to unblinding for statistical analysis. This population will be used for supportive inferences concerning efficacy.

Safety Set: All patients who are randomized and receive any amount of Study Drug. This population will be used for all safety analyses.

PK Population: All patients who are randomized and receive at least 1 dose of ISIS 678354, and have at least 1 evaluable concentration result post-first dose. This population will be used for analysis of PK data.

Analysis populations will be listed and also summarized with counts and percentages by treatment group and overall.

4.6. Demographic and Other Baseline Characteristics

Demographic data include age, age category (< 18, 18 to 64, ≥ 65 years), gender, ethnicity, race, weight, and body mass index (BMI).

Baseline characteristics include genetic confirmation and baseline lipids profile (fasting TG, apoC-III, total cholesterol, LDL cholesterol, HDL cholesterol, apoB, apoB-48, chylomicron-TG, VLDL, non-HDL-C, and apoA-1).

The following summaries will be provided:

- A summary of the demographic data, and baseline characteristics will be provided using the FAS population (Section 4.5).
- A summary of the demographic data and baseline characteristics will be provided using the PPS population (Section 4.5).
- A summary of the demographic data and baseline characteristics will be provided using the Safety Set (Section 4.5).

A by-subject listing of the demographic data and the baseline characteristics will be provided for all randomized subjects.

4.7. Medical History

The general medical history will be summarized using the Safety Set (Section 4.5). Frequency table will be provided by treatment group and overall, system organ class (SOC) and preferred term (PT), where SOC and PT are coded by Medical Dictionary for Regulatory Activities (MedDRA). The final MedDRA version used will be designated in the clinical study report.

A by-subject listing of medical history, including the reported term, the coded term, the start date, and the end date will be provided for all randomized subjects.

A separate table will be created for the targeted medical history using the Safety Set, and will include diabetes mellitus history, cardiac-related history (acute MI, percutaneous coronary intervention (PCI), CABG, unstable angina, heart failure, Stroke (CVA)/TIA, and revascularization), and pancreatitis history.

4.8. Prior and Concomitant Medication

Prior medications include medications started prior to the first dose of study medication regardless whether continued while on treatment or not. Concomitant medications include medications that patients are exposed to on or after the first dose of study medication. Partial or missing medication start date or end date will be imputed by the following imputation rules:

Start date:

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

End date: imputation will be performed for the end date only if the day or month is missing (i.e., year is present):

- 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.

Prior and concomitant medication will be summarized using the Safety Set (Section 4.5) separately. Frequency table will be provided by treatment group, anatomical therapeutic chemical (ATC) drug class and preferred term (PT), where ATC and PT are coded by World Health Organization-Drug Dictionary Enhanced (WHO-DDE). The final WHO-DDE version used will be designated in the clinical study report.

The number and percentage of patients in each of the following categories will also be summarized by treatment group using the Safety Set:

- Not taking stains at baseline
  - Initiated statins after study drug administration
- Taking statins at baseline
  - Increased statin dose or switched to higher intensity after study drug administration.

A by-subject listing of prior and concomitant medications will be provided using the Safety Set.

4.9. Efficacy Evaluation

4.9.1. Analysis and Data Conventions

4.9.1.1. Hypothesis

The study hypothesis is that ISIS 678354 can significantly improve efficacy parameters and is well-tolerated for patients with FCS. The null hypothesis for the treatment comparison will be that there is no difference between ISIS 678354 and Placebo in the percent change in fasting TG from Baseline at the primary analysis time point. The alternative hypothesis will be that there is a difference.

Symbolically, this is expressed as follows:

H(0): μ(test) = μ(reference)

H(1): μ(test) $\neq$ μ(reference)

4.9.1.2. Handling of Dropouts or Missing Data

If there is missing TG data at baseline and primary analysis time point, a two-stage multiple imputation approach will be utilized.

First, patients with a missing fasting TG at the baseline will have missing values multiply imputed based on the observed baseline assessments from other patients. The Markov Chain Monte Carlo (MCMC) method will be used to impute the missing values. The imputation model will include baseline fasting TG value and 2 stratification factors (history of pancreatitis and previous treatment with Volanesorsen) (Schafer 1997; 1999). The TG values will be natural log-transformed before the imputation process, then back transformed after imputation to create the imputed data set. The SAS procedure PROC MI will be used to create 100 imputed datasets.

The following pseudo SAS code and seed (2438291) will be used to perform the multiple imputation for missing TG at baseline:

```
proc mi data = TG seed = 2438291 nimpute = 100 out=TG2;
   transform log(baseline);
    Mcmc;
   var PANCR Volan baseline;
run;
```

The imputed baseline values will be merged with the observed post-baseline data and used for the second stage of imputation.

In the second stage of imputation, patients with a missing fasting TG at the primary analysis time point will have missing values multiply imputed based on the known assessments from the retrieved dropouts (patients who discontinue treatment before Week 23 but still have TG assessments at Weeks 23, 25, or 27), if there are a sufficient number of retrieved dropouts. The imputation model will contain the following variables: baseline fasting TG value, fasting TG values at post-baseline visits and 2 stratification factors (history of pancreatitis and previous treatment with volanesorsen), and the multiple imputation will be stratified by treatment group.

If there is no sufficient number of retrieved dropouts, missing TG value at the primary analysis time point will be imputed using a "wash-out" multiple imputation approach (Jump to Reference, J2R). With the approach, patients treated with ISIS 678354 will have missing TG values after the last dosing date multiply imputed based on baseline fasting TG, the 2 stratification factors of their own treatment group, and the imputation model for the placebo group. Patients in the placebo group will have missing TG values multiply imputed based on baseline fasting TG, fasting TG values at post-baseline visits and the 2 stratification factors from the placebo group.

The "wash-out" multiple imputation will be preformed in the following steps:

1. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute all missing values by treatment group. The variable list for imputations will include the baseline value, as well as all available post-baseline value, and stratification factors. To conform to the multivariate normality assumption, baseline, and post-baseline fasting lipid data will be natural log-transformed before the imputation process, and the variable values will be back transformed to create the imputed data set. The SAS procedure PROC MI will be used in the multiple imputation. The MCMC method will impute primary analysis time point data for each of the 100 datasets from the first imputation stage. EM algorithm will be used to derive a set of initial parameter estimates for MCMC method. A non-informative prior (Jeffreys' prior) will be used to derive the posterior distribution of the parameters. A total of 100 imputed datasets will be created from the above 2-stage multiple imputation process.

   The following pseudo SAS code and seed (2438291) will be used to perform the multiple imputation for each treatment group:

```
proc mi data = TG2 seed = 2438291 nimpute = 1;
   transform log(baseline) log(week5) log(week9) log(month3)
   log(week21) log(month6) log(week29) log(week37) log(week45)
   Log(month12);
    mcmc;
   var PANCR Volan baseline week5 week9 month3 week21 month6
    week29 week37 week45 month12;
    by _imputation_;
run;
```

   If there is no missing data at baseline, then the baseline imputation will not be performed. The second stage of imputation will be performed to create 100 imputed datasets.

2. A general linear model will be fitted using the data in the placebo group for each imputed dataset
3. For patients in both ISIS 678354 dose groups, the imputed values after last dose date will be replaced with the values imputed using J2R method (calculated using the patients' own baseline fasting TG, the 2 stratification factors, and the model from step 2)
4. The variable values will be back transformed from nature log scale to the original scale in the final imputed datasets.

For each of the 100 imputed datasets, the endpoint will be compared between ISIS 678354 treatment groups and pooled placebo using an ANCOVA model for continuous endpoints or logistic regression for binary endpoints as described in the primary analysis for each endpoint. The estimates from the 100 fitted models will be combined to provide an overall estimate with corresponding confidence intervals and p-value (Little & Rubin 2002)

The following pseudo SAS code will be used to estimate corresponding confidence intervals and p-value:

```
proc mianalyze data=diff;
   modeleffects estimate;
   stderr stderr;
run;
```

For the continuous endpoints, the treatment difference and the corresponding 95% CI will be presented. For the analyses using logistic regression, the odds ratio and the corresponding 95% CI will be presented.

Missing values at Months 3 and 12 and other lipid parameters will be imputed in a similar way to the primary analysis time point.

Only observed lipid data will be displayed in the data listings.

4.9.1.3. Multiplicity

To control the overall Type I error rate at 0.05 across the primary endpoints and secondary endpoints for the final analysis, the gatekeeping testing strategy will be applied to the primary endpoint family and secondary endpoint family. The hierarchical testing procedure will be utilized within the primary endpoint family and secondary endpoint family.

For the primary endpoint family, the 2 treatment arms will be compared against pooled placebo using the hierarchical testing procedure, in which the ISIS 678354 80 mg treatment group will be compared to the pooled placebo at the 2-sided alpha level of 0.05, if the comparison is statistically significant ($p < 0.05$), then the ISIS 678354 50-mg treatment group is compared against the pooled placebo at the alpha level of 0.05. If the comparison of the ISIS 678354 80-mg treatment group is not statistically significant, then the comparison of the ISIS 678354 50-mg treatment group against pooled placebo and all secondary endpoints will be considered exploratory.

Testing of secondary endpoint family will be performed only if the comparison of the primary endpoint is statistically significant ($p < 0.05$) for both ISIS 678354 80-mg and 50-mg treatment groups. Testing of the secondary endpoint family will be conducted according to the following sequence:

- Secondary endpoint 1: comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 2: comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 3: comparison of percent change in fasting apoC-III from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 4: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 5: comparison of percent change in fasting apoB-48 from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 6: comparison of percent change in fasting non-HDL-C from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 7: comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 8: comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 9: comparison of percent change in fasting apoC-III from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 10: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 11: comparison of percent change in fasting apoB-48 from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 12: comparison of percent change in fasting non-HDL-C from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 13: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening
- Secondary endpoint 14: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in FAS
- Secondary endpoint 15: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening

- Secondary endpoint 16: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the FAS
- Secondary endpoint 17: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 18: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 19: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 20: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in the FAS
- Secondary endpoint 21: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 22: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 23: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between ISIS 678354 50-mg treatment group and pooled placebo in FAS
- Secondary endpoint 24: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in the FAS
- Secondary endpoint 25: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Secondary endpoint 26: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled ISIS 678354 treatment group and pooled placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Secondary endpoint 27: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS
- Secondary endpoint 28: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between ISIS 678354 50-mg treatment group and pooled placebo in FAS

If the comparison of the first secondary endpoint is statistically significant ($p < 0.05$), then the second secondary endpoint will be tested. However, if the comparison of the first secondary endpoint is not statistically significant, then all endpoints of lower rank will be considered exploratory. This process is repeated with each subsequent secondary endpoint.

4.9.1.4. Interim Analyses

There is no interim analysis planned for the study.

4.9.1.5. Examination of Subgroups

To evaluate the consistency of analysis results in the primary endpoint over parameters such as demographic and baseline characteristics, exploratory subgroup analyses will be performed if supported by data. The subgroups include but not limited to:

- Gender: Male, Female
- Prior history of pancreatitis within 10 years prior to Screening: Yes vs. No
- Previous treatment with Volanesorsen: Yes vs. No
- Region: North America, Europe (including United Kingdom), United States
- Age: < 65 years, ≥ 65 years
- Race: White vs. non-White
- Ethnicity: Hispanic or Latino vs. Not Hispanic or Latino
- Diabetic status: No vs. Type I or Type II
- Baseline TG: < median vs. ≥ median

4.9.2. Primary Efficacy Variable

The primary efficacy analysis will take place after the last patient has completed the Week 53/ET visit and the database has been locked, and will be based on the percent change from Baseline in fasting TG at primary analysis time point.

The primary endpoint is the percentage change in fasting TG from Baseline to the primary analysis time point. The primary analysis of the primary endpoint is to compare the percent change from Baseline to the primary analysis time point in fasting TG between each ISIS 678354 treatment group (ISIS 678354 80 mg, ISIS 678354 50 mg) vs. pooled placebo using an ANCOVA model in the FAS. The ANCOVA model will use precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with Volanesorsen (yes vs. no) and treatment group (ISIS 678354 80 mg, ISIS 678354 50 mg, placebo) as the fixed effects and nature log-transformed baseline fasting TG as a covariate. To account for potential heterogeneity in variance, the 95% CIs will be calculated using the robust variance estimator based on the Bell and McCaffrey method (Imbens & Kolesár 2016).

If patients have intercurrent event(s) before Week 23, e.g., treatment discontinuation, use of additional medication, changes in background or concomitant treatments, the Treatment Policy strategy will be implemented, the patients' assessments post intercurrent events will continue to be collected. All assessments including those post the intercurrent events will be utilized in the analysis.

Patients with missing TG value at the baseline and/or primary analysis time point will have fasting TG value multiply imputed using the multiple imputation methods described in Section 4.9.1.2 in the SAP. The are provided in the table below:

Table 1: Attributes and Description of the Estimands

Treatments	ISIS 678354 80 mg Pooled placebo
Participant Population	Patients with FCS as defined by protocol eligibility criteria
Variable	Percent change from Baseline to primary analysis time point (average of Weeks 23, 25 and 27) in fasting TG
Intercurrent events (ICEs) and strategies	Discontinuation of study treatment prior to Week 23 *Treatment policy strategy* Disallowed concomitant therapy/procedure prior to Week 23 *Treatment policy strategy*
Population-level summary	Difference in means between ISIS 678354 80 mg and pooled placebo in the FAS
Description of estimand	The difference in means for percent change from Baseline to the primary analysis time point in fasting TG between ISIS 678354 80 mg and pooled placebo (regardless of early treatment discontinuation, use of additional medication, or change in background or concomitant treatments) in patients with FCS

Treatments	ISIS 678354 50 mg Pooled placebo
Participant Population	Patients with FCS as defined by protocol eligibility criteria
Variable	Percent change from Baseline to primary analysis time point (average of Weeks 23, 25 and 27) in fasting TG
Intercurrent events (ICEs) and strategies	Discontinuation of study treatment prior to Week 23 *Treatment policy strategy* Disallowed concomitant therapy/procedure prior to Week 23 *Treatment policy strategy*
Population-level summary	Difference in means between ISIS 678354 50 mg and pooled placebo in the FAS
Description of estimand	The difference in means for percent change from Baseline to the primary analysis time point in fasting TG between ISIS 678354 50 mg and pooled placebo (regardless of early treatment discontinuation, use of additional medication, or change in background or concomitant treatments) in patients with FCS

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

```
**************************************************************************
* Note:
*   baseline = baseline TG
*    impute = the iteration number in the multiple imputation
*   TRTN = Treatment group: 0=Placebo, 1= ISIS 678354 50 mg, 2 = ISIS 678354 80 mg
*    PANCR = Prior history of pancreatitis within 10 years prior to Screening: 0 = No, 1 =
Yes
*    VOLAN= Previous treatment with Volanesorsen: 0= No, 1= Yes
*    BM_stderr= Bell and McCaffrey standard error
**************************************************************************
        data TG; set TG;
           LOGBASE = LOG(baseline);   /* log transformed baseline*/

        proc mixed data = TG;
           by _impute;
           class TRTN PANCR VOLAN;
           model PCHG = TRTN PANCR VOLAN LOGBASE;
           lsmeans TRTN/e diff cl;
           estimate 'ISIS 678354 50 mg vs Placebo' TRTN -1 1 0;
           estimate 'ISIS 678354 80 mg vs Placebo' TRTN -1 0 1;
        run;
```

The estimates from the fitted models for each of the 100 imputed datasets will be combined to provide an overall estimate with corresponding confidence intervals and p-value (Little & Rubin 2002). The following pseudo SAS code will be used to estimate corresponding confidence intervals and p-value:

```
        proc mianalyze data=diff;
           modeleffects estimate;
           stderr BM_stderr;
        run;
```

The following sensitivity analyses of the primary endpoint will be conducted to assess the robustness of the primary analysis result.

Sensitivity Analysis 1: PPS

The primary efficacy analysis with ANCOVA model for percent change in fasting TG from Baseline to the primary analysis time point described above will be repeated in the PPS.

Sensitivity Analysis 2: Completer Set (Subset of FAS)

The primary efficacy analysis with ANCOVA model for percent change in fasting TG from Baseline to the primary analysis time point will be repeated in the subset of the patients in the FAS with no missing TG values at the primary analysis time point.

Sensitivity Analysis 3: Exploring the robustness of the primary analysis (FAS)

Additional sensitivity analyses using different imputation approach with ANCOVA model will be conducted in the FAS to assess the robustness of the primary analysis results.

1. Patients with missing TG value at the primary analysis time point will be imputed using a pattern mixture model. Specifically, for patients treated with ISIS 678354 who discontinue the treatment due to AE or lack of efficacy (i.e., informative missing), their missing fasting TG data after the last dosing date will be multiply imputed using the copy increment from reference (CIR) approach based on the estimates from of the placebo patients. The CIR approach is detailed in (Carpenter *et al.* 2013). The assumption is when a patient discontinues treatment due to informative missing, from withdrawal onwards he/she would progress in the same way as the patients in the placebo group. For patients who discontinue due to other reasons and all patients from the placebo group, their missing data will be treated as non-informative missing, and data will be multiply imputed based on the distribution of their own treatment group.
2. All patients treated with ISIS 678354 will have missing TG values after the last dosing date multiply using the CIR approach based on the estimates from the placebo patients. Missing TG values for placebo patients will be imputed based on the distribution of the placebo group.

Sensitivity Analysis 4: Non-parametric analysis with Wilcoxon rank-sum test (FAS)

A nonparametric Wilcoxon rank-sum test will be performed on the percent change in fasting TG from baseline to the primary analysis timepoint in the FAS. Missing data will be handled using the same multiple imputation method as the primary analysis. The estimates for each of the 100 imputed datasets will be combined to provide an overall Hodges-Lehmann estimator of the location shift and corresponding 95% CI between each ISIS 678354 treatment groups group and the pooled placebo group.

Sensitivity Analysis 5: Tipping point analysis (FAS)

An additional sensitivity analysis using the 2-dimensional tipping-point approach will be conducted in the FAS to assess the impact of missing data on the result of the primary analysis.

The sensitivity analysis will be conducted as follows using the imputed data based on the primary imputation approach as described in Section 4.9.1.2 in the SAP:

1. For the placebo group, a positive constant shift (δ_c) will be added to or subtracted from percent change of the imputed TG values at the primary time point. The shift will be gradually increased
2. For each value of the placebo shift parameter, a positive constant shift (δ_t) will be added to or subtracted from percent change of the imputed TG values at the primary time point in the active treatment groups. The shift will be increased in a repeated process until the treatment effect is no longer significant at 0.05 level in step 5 below.
3. For each of the 100 imputed datasets, the same ANCOVA model as described for the primary analysis of the primary endpoint will be fitted to estimate treatment differences and standard errors.
4. The 100 sets of estimates will be combined with SAS PROC MIANALYZE as described in Section 4.9.1.2 in the SAP
5. Steps 1 to 4 will be repeated with different values of the shift parameters until the tipping points are reached.

Values of δ_c and δ_t will be determined post-hoc in order to define reasonable increments.

Sensitivity Analysis 6: ANCOVA model using log-transformed data (FAS)

The percent change from Baseline to the primary analysis time point in fasting TG between each ISIS 678354 treatment group (ISIS 678354 80 mg, ISIS 678354 50 mg) vs. pooled placebo will be compared using ANCOVA model with log(y/x) as dependent variable, where y is the value of fasting TG at primary analysis time point, x is the baseline value of fasting TG; and the two randomization stratification factors and treatment group as factors and nature log-transformed baseline fasting TG as a covariate. The model will provide an estimate of log post-baseline to baseline ratio for each treatment group as well as the ratios relative to the pooled placebo group and the corresponding 95% confidence intervals (CIs). The log post-baseline to baseline ratios will be converted back to the original ratio scale. The percent change from baseline for each treatment group will then be calculated based on the estimated ratio as 100% * (ratio –1). Similarly, the estimated upper and lower CIs for the ratio can be calculated as 100% * (CI –1). Patients with missing fasting TG value at the baseline and/or primary analysis time point will have TG value multiply imputed using the multiple imputation methods described in Section 4.9.1.2 in the SAP.

Descriptive statistics and other data presentation

Descriptive statistics and cumulative distribution curves will be provided for observed fasting TG levels and percent change in fasting TG in each treatment group for the primary endpoint.

4.9.3. Secondary Efficacy Variables

In order to control the type I error, a sequential closed testing procedure will be employed with the sequence of endpoints defined as in Section 4.9.1.3 above. Testing of secondary endpoints will be performed only if the treatment comparison of the primary analysis of the primary endpoint is statistically significant ($p < 0.05$) for both ISIS 678354 80-mg and 50-mg treatment groups. Testing of the secondary endpoints will be conducted according to the following sequence: if the primary analysis of the first secondary endpoint (comparison of percent change in fasting TG from Baseline to Month 12 between ISIS 678354 80-mg treatment group and pooled placebo in FAS) is statistically significant ($p < 0.05$) then the second secondary endpoint (comparison of percent change in fasting apoC-III from Baseline to the primary analysis time point between ISIS 678354 80-mg treatment group and pooled placebo in FAS) will be tested. However, if the treatment comparison based on the first secondary endpoint is not statistically significant, then all endpoints of lower rank will be considered exploratory. This process is repeated with each subsequent secondary endpoint.

4.9.3.1. Percentage Change from Baseline in Fasting TG at Month 12

The percent change in fasting TG from Baseline to Month 12 in the FAS will be analyzed in the same way as the primary analysis of the primary endpoint. The intercurrent events will be handled using the Treatment Policy strategy.

A 2-dimensional tipping-point analysis will be conducted in the FAS as a sensitivity analysis.

Descriptive statistics and cumulative distribution curves will be provided for observed fasting TG levels and percent change in TG in each treatment group at Month 12.

4.9.3.2. Proportion of Patients who Achieve ≥ 40% Reduction in Fasting TG from Baseline at the Primary Analysis Time Point

The proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point in the FAS will be compared between each ISIS 678354 treatment group and placebo group using a logistic regression model with the 2 randomization stratification factors and treatment group as the factors, and nature log-transformed baseline fasting TG as a covariate. Missing TG values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. The estimates from the fitted model for each of the 100 imputed datasets will be combined to provide an overall odds ratio with corresponding confidence intervals and p-value. The intercurrent events will be handled using the Treatment Policy strategy.

Sensitivity Analysis 1: An additional analysis will be conducted in the FAS, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

Sensitivity Analysis 2: A 2-dimensional tipping-point analysis will be conducted in the FAS using the imputed data based on the primary imputation approach as described in Section 4.9.1.2 in the SAP.

4.9.3.3. Percentage Change from Baseline in Fasting apoC-III, apoB-48, and non-HDL-C at Primary Analysis Time Point (Months 6) and Month 12

The percent change in fasting apoC-III, apoB-48, and non-HDL-C from Baseline to the primary analysis time point and Month 12 in the FAS will be analyzed in the same way as the primary analysis of the primary endpoint. The same multiple imputation method as the primary analysis of the primary endpoint will be used for imputing missing data. The intercurrent events will be handled using the Treatment Policy strategy. A 2-dimensional tipping-point analysis will be conducted in the FAS as a sensitivity analysis for each parameter.

4.9.3.4. Proportion of Patients who Achieve Fasting TG ≤ 880 mg/dL at Primary Analysis Time Point

The proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point will be analyzed in the same way as the proportion of patients who achieve ≥ 40% reduction in fasting TG. Missing TG values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. The analysis will be conducted in the subset of FAS with baseline fasting TG > 880 mg/dL. The intercurrent events will be handled using the Treatment Policy strategy.

Sensitivity Analysis 1: An additional analysis will be conducted in the subset of FAS with baseline fasting TG > 880 mg/dL, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

Sensitivity Analysis 2: A 2-dimensional tipping-point analysis will be conducted in the subset of FAS with baseline fasting TG > 880 mg/dL using the imputed data based on the primary imputation approach as described in Section 4.9.1.2 in the SAP.

4.9.3.5. Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 in the Subset of FAS with a prior history of pancreatitis within 10 years prior to Screening

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 and as outlined in the Acute Pancreatitis Adjudication Committee (PAC) Charter. These events will be categorized by the various criteria to be one of the following: 1) documented pancreatitis, 2) probable pancreatitis, 3) possible pancreatitis, 4) unable to adjudicate and

5) no diagnosis of acute pancreatitis. In the event of any discrepancies between the categories in this SAP and the final data transfer, the categories in the final data transfer will be used. For the purposes of data analysis, events that are documented, probable or possible are to be considered adjudicated acute pancreatitis. A listing will be provided to display each adjudicator's and the final adjudication committee's classification results for each event. The number and percentage of subjects and the number of events within each classification, by each adjudicator and by final adjudication committee respectively, will be summarized. In addition, the number and percentage of cases where the adjudicator's individual categorization of the event was discordant will be provided. The summaries be conducted in the FAS.

The adjudicated acute pancreatitis event rate from Week 1 to Week 53 in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening will be compared between pooled ISIS 678354 treatment and placebo group using a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment, i.e., events occurred within 1826 days (calculated by 365.25 times 5 and rounded to integer) before the first dose date and up to the first dose date and time, as a covariate. The logarithm of time in year that each patient was observed from Week 1 to Week 53 will be used as an offset variable. From the models, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratio relative to the placebo group and corresponding 95% confidence intervals will be estimated. The p-value of Wald-based chi-square test will also be reported.

Week 53 is defined as Day 379 (scheduled visit day plus a 14-day window) or last contact date within the study, whichever is earlier. If patients have intercurrent event(s) before Week 53, the Treatment Policy strategy will be implemented, the pancreatitis events occurred post intercurrent events will continue to be collected. All adjudicated pancreatitis events including those post the intercurrent events will be included in the analysis. For patients who discontinued the treatment early and were lost to follow-up before Week 53, the pancreatitis event rate will be adjusted by the length of observation time in the analysis model.

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

*** TRTN = Treatment group: 0=Placebo, 1= ISIS 678354 50 mg or ISIS 678354 80 mg**
*** VOLAN= Previous treatment with Volanesorsen: 0= No, 1= Yes**
*** NUMEVENT = number of adjudicated acute pancreatitis events**
*** NUM5YEAR = number of adjudicated acute pancreatitis events in 5 years prior to the enrollment**

```
data Pan; set Pan;
   Logtime = LOG(years);    /* log transformed time*/
proc genmod data = pan;
   class TRTN VOLAN;
   model NUMEVENT = TRTN VOLAN NUM5YEAR/dist=negbin link = log
                    offset = logtime;
   lsmeans TRTN/diff cl exp ilink;
run;
```

If the Negative Binomial regression model does not converge, a Poisson regression model with Pearson chi-square scaling of standard errors to account for potential overdispersion will be used instead of the Negative Binomial regression model. The model will include the same factors and covariate as the Negative Binomial regression model.

If one treatment group has no event, instead of using Negative Binomial or Poisson regression model on the number of events, the proportion of patients with adjudicated acute pancreatitis will be compared between pooled ISIS 678354 treatment group and placebo group using a Fisher's Exact test. The odds ratio, corresponding 95% CI, and p-value will be reported.

Additional dot plots by treatment group will be provided for pancreatitis attacks, grouped by number of previous attacks in the last 5 years.

4.9.3.6. Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 in the FAS

The data will be analyzed in the same way as described in Section 4.9.3.5.

Additional dot plots will be by treatment group provided for pancreatitis attacks, grouped by number of previous attacks in the last 5 years.

4.9.3.7. Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 in the Subset of FAS with a prior history of pancreatitis within 10 years prior to Screening

The data will be analyzed in the same way as described in Section 4.9.3.5.

4.9.3.8. Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 in the FAS

The data will be analyzed in the same way as described in Section 4.9.3.5.

4.9.3.9. Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 in the Subset of FAS with ≥ 2 Events of Adjudicated Acute Pancreatitis in 5 years Prior to Enrollment

The data will be analyzed in the same way as described in Section 4.9.3.5. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.

4.9.3.10. Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 in the Subset of FAS with ≥ 2 Events of Adjudicated Acute Pancreatitis in 5 years Prior to Enrollment

The data will be analyzed in the same way as described in Section 4.9.3.5.

4.9.3.11. Proportion of Patients who Achieve Fasting TG ≥ 70% Reduction from Baseline at Primary Analysis Time Point

The proportion of patients who achieve fasting TG ≥ 70% reduction at the primary analysis time point in the FAS will be analyzed in the same way as the proportion of patients who achieve ≥ 40% reduction in fasting TG. Missing TG values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. The intercurrent events will be handled using the Treatment Policy strategy.

Sensitivity Analysis 1: An additional analysis will be conducted in the FAS, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

Sensitivity Analysis 2: A 2-dimensional tipping-point analysis will be conducted in the FAS using the imputed data based on the primary imputation approach as described in Section 4.9.1.2 in the SAP.

4.9.3.12. Proportion of Patients who Achieve Fasting TG ≤ 500 mg/dL at Primary Analysis Time Point

The proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point will be analyzed in the same way as the proportion of patients who achieve ≥ 40% reduction in fasting TG. Missing TG values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. The analysis will be conducted in the subset of FAS with baseline fating TG > 500 mg/dL. The intercurrent events will be handled using the Treatment Policy strategy.

Sensitivity Analysis 1: An additional analysis will be conducted in the subset of FAS with baseline fasting TG > 500 mg/dL, in which all patients who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

Sensitivity Analysis 2: A 2-dimensional tipping-point analysis will be conducted in the subset of FAS with baseline fasting TG > 500 mg/dL using the imputed data based on the primary imputation approach as described in Section 4.9.1.2 in the SAP.

4.10. Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

Risk difference and corresponding 95% CI in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group in selected safety endpoint will be provided. The crude incidence rate (or percentage) is defined as the number of patients who experienced at least one event times 100 divided by the total number of patients. The 95% CI of risk difference in crude incidence rate will be estimated using the Miettinen-Nurminen (MN) method.

4.10.1. Extent of Exposure

The exposure to treatment will be presented in terms of the duration of exposure (in days), number of doses administered, and amount of Study Drug received for each patient. The duration of exposure will be calculated as the last dose date minus the first dose date plus 28 days (one dose interval) for each patient. Treatment duration, number of doses, and amount of Study Drug received will be summarized by treatment group.

Compliance with Study Drug administration will be summarized by descriptive statistics by treatment group.

The evaluation of compliance of ISIS 678354 will be done using the following formula:

Actual total dose injected (mg) *100/Expected total dose (mg) to be administered.

The evaluation of compliance of placebo will be done using the following formula:

Actual total volume injected (mL) *100/Expected total volume (mL) to be administered.

Patients in Cohort A will receive 50 mg of ISIS 678354 once every 4 weeks or matching volume of placebo (0.5 mL) Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg ISIS 678354 once every 4 weeks or matching volume of placebo (0.8 mL) Weeks 1-49 of the Treatment Period.

For early withdrawals/terminations, the total dose injected will be calculated for the period up to their withdrawal/termination.

The following summaries will be provided:

- A summary of the duration, number of doses administered and the total amount of study drug by treatment group
- A summary of percent compliance by treatment group.
- Number of patients with dose interruption due to AE and number of patients with study drug reduced due to AE.
- A summary of number of days of dose interruption.

The following listings will be provided:

- A by-subject listing of administration of study drug
- A by-subject listing of treatment compliance

4.10.2. Adverse Events

All adverse events will be coded by the MedDRA coding system. The final version used will be designated in the clinical study report.

The following imputation rules will be applied to impute start dates under conservative principles:

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

Imputation will be performed 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.

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of study drug and subsequently worsens, or is not present prior to receiving the first dose of study drug but subsequently appears.

In addition, if the severity of an AE changes during the study, a separate AE will be recorded for each severity on the AE CRF. The "first" and "second" AE records will be identified based on the AE start date. AE start date of the second record will be the AE stop date of first record. These linked events should be compared pairwise. Consider the following two cases, where the AE severity (mild/moderate/severe) and seriousness (Yes/No) between the two records in a pair are compared.

Case 1: The first AE record in the pair occurs before the first dosing, and the second AE record occurs after the first dosing.

If the AE severity or seriousness of the second record is worse than that of the first record, then only the second AE is deemed as a TEAE. Otherwise, neither record is considered as TEAE.

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

The worst AE is considered as a TEAE.

- The frequency of patients with any incidence of AEs and the number events will be summarized by MedDRA preferred term and system organ class for:
- Any TEAE
- TEAEs potentially related to Study Drug. Related is defined as "Related", "Possible", or missing relationship to Study Drug
- Any treatment-emergent adverse event by severity. At each level of patient summarization, a patient is classified according to the worst reported severity if the patient reported one or more events. Adverse events with missing severity will be categorized as "Missing" for this summary.
- TEAEs potentially related to Study Drug by severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to death
- Serious TEAEs
- Serious TEAEs potentially related to Study Drug
- TEAE with an incidence rate > 5% in any treatment groups
- Non-serious TEAE with an incidence rate > 5% in any treatment groups

Adverse event summaries will be presented alphabetically by SOC and preferred term (PT) and by descending frequency. An overview of AEs will be provided for all TEAes. AEs that lead to treatment discontinuation, and AEs that lead to death will be listed.

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

4.10.3. Adverse Events of Special Interest

The following events are considered AE of special interest and will be summarized:

- Platelet count reduction to levels below 50,000/mm^3 accompanied by a major bleeding event (MB) or clinically relevant non-major bleeding (CRNMB) event or platelet count reduction to levels below 25,000/mm^3, irrespective of bleeding status
- Requirement of any use of medications (such as antihistamines, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroids, etc.) as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction.

The number and percentage of patients experiencing events as well as the total number of reported events, classified by SOC and PT, will be tabulated by treatment group.

The following additional analyses may be provided if supported by data:

- A cumulative incidence plot
- Risk difference and its 95% CI in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group. The analysis methods are detailed in Section 4.10 of this SAP.
- Exposure adjusted incidence rates (EAIRs) and risk difference (or ratio) in EAIRs may also be provided, if deemed necessary. EAIR is defined as the number of patients who experienced at least one event times 100 divided by total patient-years at risk for the event. For patients with events, the time at risk is the time from the first dose date to the first onset of an event (i.e., first event date minus first dose date plus one day divided by 365.25); for patients with no event, the time at risk is the total duration in the on-study period (i.e., last participation date minus first dose date plus one day divided by 365.25).
- Exposure adjusted event rates (EAERs), defined as the number of events times 100 divided by the total duration in the on-study period in year.

4.10.4. Other Events of Interest

4.10.4.1. Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe adverse events with the preferred terms (PTs) including Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection, persisted for at least two days (i.e., event onset date on the day of injection and resolution date not on the day of injection or the day after injection) or ongoing; or (B) any AE at the Study Drug injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the Study Drug injection site is the principal reason for discontinuation. LCRIS will be summarized using the MedDRA coding system, by PT and by treatment group. Patients with moderate, severe and any LCRIS will also be summarized. Discontinuations due to AE at the injection site will be summarized separately.

Percentage of injections leading to LCRIS will be summarized by PT and overall using the descriptive statistics. Additionally, percentage of injections leading to events will be summarized by moderate, severe severity and overall discontinuation of Study Drug due to AE at injection site.

Percentage of injections leading to LCRIS will be calculated as follows for each patient: (A/B)*100, where A = number of injections with a LCRIS, and B = total number of injections. Doses that are split across multiple injections are counted as a single injection.

The duration to resolution of a LCRIS will be summarized descriptively by treatment group and total ISIS 678354 treated. If there are multiple LCRIS related to an injection and no overlap between events, the duration will be calculated as the sum of the duration of all LCRIS that are related to the injection. If there are overlaps, the duration will be calculated using the earliest start date and latest stop date of all LCRIS that are related to the injection. For unresolved LCRIS with missing stop date, the last participation date will be used in the calculation.

In addition, for patients who experienced LCRIS, time to onset of the first event, the number of injections prior to the first LCRIS will also be summarized descriptively by treatment group and total ISIS 678354 treated.

LCRIS will also be listed.

4.10.4.2. Injection Site Reaction

Injection site reaction (ISR) is defined as any AE with PT or verbatim term containing 'Injection Site' that persisted for at least two days (i.e., event resolution date not on the day of the event onset date or the day after) or ongoing. ISR will be summarized using the MedDRA coding system, by PT and by treatment group.

Percentage of injections leading to ISRs will be summarized by PT and overall using the descriptive statistics.

Percentage of injections leading to ISR will be calculated as follows for each patient: (A/B)*100, where A = number of injections with an ISR, and B = total number of injections. Doses that are split across multiple injections are counted as a single injection.

The duration to resolution of an ISR will be summarized descriptively by treatment group and total ISIS 678354 treated. If there are multiple ISRs related to an injection and no overlap between ISRs, the duration will be calculated as the sum of the duration of all ISRs that are related to the injection. If there are overlaps, the duration will be calculated using the earliest start date and latest stop date of all ISRs that are related to the injection. For unresolved ISRs with missing stop date, the last participation date will be used in the calculation.

In addition, for patients who experienced ISR, time to onset of the first event, the number of injections prior to the first ISR will also be summarized descriptively by treatment group and total ISIS 678354 treated.

ISR will also be listed.

4.10.4.3. Flu-like Reactions

Flu-like reactions (FLR) will be evaluated using the following 2 definitions:

Definition 1 (FLR 1): defined as adverse events with PTs including Influenza like illness, Pyrexia, Feeling hot, Body temperature increased, Chills, Myalgia, or Arthralgia, starting on the day of injection or next day.

Definition 2 (FLR 2): defined as adverse events with PTs including either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, plus at least two of the following symptoms with the PTs: Chills, Myalgia, or Arthralgia, starting on day of injection or the next day.

Flu-like reactions will also be summarized using the MedDRA coding system, by preferred term and by treatment group.

Percentage of injections leading to flu-like reactions will be summarized by treatment group using the descriptive statistics.

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

For the subset of patients experiencing FLR(s), the time to onset of first FLR will be summarized using descriptive statistics.

Flu-like reactions will also be listed.

4.10.4.4. Bleeding TEAE

Bleeding TEAEs will be analyzed for the following categories. The number and percentage of patients experiencing events as well as the number of reported events, classified by SOC and PT, will be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided.

- Bleeding TEAEs (defined based on the 'Haemorrhages' Standardized MedDRA Query [SMQ, both narrow and broad scope])
- Clinical bleeding TEAEs, i.e. bleeding TEAEs excluding events at the injection site and events related to a laboratory value
- Clinical bleeding events with concomitant anticoagulant or antiplatelet medication
- Clinical bleeding events without concomitant anticoagulant or antiplatelet medication

4.10.4.5. Thrombocytopenia TEAE

The number and percentage of patients experiencing events as well as the number of reported events, classified by PT, will be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total olezarsen) and pooled placebo group will be provided.

- Thrombocytopenia TEAE (defined based on the 'Thrombocytopenias' High Level Terms [HLT] or 'Platelet count decreased' PT)

4.10.4.6. Hypersensitivity TEAE

Hypersensitivity TEAEs will be analyzed for the following categories. The number and percentage of patients experiencing events will be tabulated by treatment group. The risk difference (and 95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will also be provided.

- Hypersensitivity TEAE (defined based on the Hypersensitivity SMQ [narrow scope only]) by SOC and PT
- TEAEs in the Hypersensitivity FMQ (narrow) by PT
- Serious TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuation in the Hypersensitivity FMQ (narrow) by PT
- Action taken with drug due to TEAEs in the Hypersensitivity FMQ (narrow)
- Rescue medication used in management TEAEs in the Hypersensitivity FMQ (narrow)
- TEAEs in the Hypersensitivity FMQ (broad) by PT
- Serious TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuation in Hypersensitivity FMQ (broad) by PT
- Action taken with drug due to TEAEs in the Hypersensitivity FMQ (broad)
- Rescue medication used in management TEAEs in Hypersensitivity FMQ (broad)
- TEAEs in the Hypersensitivity algorithmic FMQ. The FMQ definition is using an algorithmic component of the PTs identified within the Hypersensitivity FMQ based on the locations that hypersensitivity is known to commonly affect, i.e., airway, skin, soft tissue, and systemic. In addition, the onset of event(s) is within 7 days of the treatment.
- TEAEs in the Anaphylactic reaction FMQ (narrow) by PT
- Serious TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuation in Anaphylactic reaction FMQ (narrow) by PT

For patients who had hypersensitivity reactions, either in FMQ narrow, broad, or algorithmic, the time to onset of the first event will be summarized using descriptive statistics

For patients who had serious hypersensitivity reactions or discontinued study drug due to hypersensitivity reactions, either in FMQ narrow, broad, or algorithmic, a graphical patient profile will be provided.

4.10.4.7. Renal Impairment TEAE

Renal impairment TEAEs will be analyzed for the following categories. The number and percentage of patients experiencing events will be provided. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided.

- Renal impairment TEAEs (defined based on the ‘Acute renal failure’ SMQ (narrow and broad))
- TEAEs, serious TEAEs, fatal TEAEs, and TEAEs leading to treatment discontinuation in the AKI FMQ (narrow) by PT
- TEAEs, serious TEAEs, fatal TEAEs, and TEAEs leading to treatment discontinuation in the AKI FMQ (broad) by PT

For patients who had treatment emergent proteinuria (defined as all events fall under proteinuria SMQ narrow and broad), the time to onset of the first event will be summarized using descriptive statistics.

For patients who had treatment emergent albuminuria (defined as all related events fall under proteinuria SMQ narrow, including diagnosis tests for albumin/creatinine ratio), the time to onset of the first event will be summarized using descriptive statistics.

For patients who had AKI TEAE (FMQ narrow or broad), the time to onset of the first event will be summarized using descriptive statistics.

For patients who had serious AKI TEAE (FMQ narrow or broad), or discontinued study drug due to AKI TEAE (FMQ narrow or broad), a data listing including eGFR and serum creatinine and a graphical patient profile will be provided.

4.10.4.8. Abnormal Liver Function TEAE

Abnormal liver function TEAEs will be analyzed for the following categories. The number and percentage of patients experiencing events tabulated by treatment group. The risk difference (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided.

- Abnormal liver function TEAE (defined based on the 'Drug related hepatic disorders – comprehensive search' SMQ (narrow and broad))
- TEAEs, Serious TEAEs, drug-related TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuation in Hepatic Injury and Hepatic Failure FMQ (narrow)
- TEAEs in Hepatic Injury and Hepatic Failure FMQs (narrow) by PT
- Discontinuations and Lost to follow-up with Liver Safety Lab Elevation or AEs (in Hepatic FMQs)

4.10.5. Clinical Laboratory Evaluation

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

- Chemistry: sodium, potassium, chloride bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, glucose, BUN, creatinine, uric acid, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, ALT, AST, ALP, creatine kinase, and GGT.
- Hematology: red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, 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 (inflammatory), HOMA-IR, fructosamine, glycated hemoglobin (HbA_{1c}), glycated albumin
- Screening Tests: hepatitis B surface antigen, hepatitis C antibody, HIV antibody, FSH (women), serum βhCG (women). The screening test data will only be displayed in patient listings

- Urinalysis: color, appearance, specific gravity, pH, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocytes esterase, nitrate, and microscopic examination. The expanded urinalysis data will be only displayed in patient listings. Urine albumin/creatinine ratio (UACR) and protein/creatinine ratio (UPCR) will be summarized.

All safety lab data will also be displayed in patient listings based on all randomized patients. Chemistry, hematology, coagulation, other assessments, selected urinalysis, and selected lipid parameters including LDL-C and apoB (result, change and percent change from Baseline) will be summarized using descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum and maximum) by treatment group and study visit.

A frequency bar chart of the missing data and existing data at each visit for patients remaining in the trial will be provided for creatinine, BUN, total bilirubin, ALT, AST, ALP, estimated Glomerular Filtration Rate (eGFR), hsCRP, hemoglobin, hematocrit, platelets, white blood cells, UACR, UPCR.

Additional analyses of key safety laboratory data

The following analyses of key safety laboratory data will be provided.

Hepatobility Laboratory Abnormalities:

The number and percent of patients falling in each of the following categories based on results after first dose will be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided for selected categories.

- ALT or AST≥ ULN
- The higher of ALT/AST ≥ 3 × upper limit of normal (ULN) or ALT/AST ≥ 2 × Baseline (i.e., ALT/AST ≥ 3 × ULN and ALT/AST ≥ 2 × Baseline)
- ALT/AST ≥ 3 × ULN
- ALT/AST ≥ 5 × ULN
- ALT/AST ≥ 8 × ULN
- ALT/AST ≥ 10 × ULN
- ALT/AST ≥ 20 × ULN
- Highest ALT falling in: ≥ 3 × ULN - < 5 × ULN, ≥ 5 × ULN - < 10 × ULN, ≥ 10 × ULN -< 20 × ULN (the risk difference will not be provided for this category)
- Total bilirubin ≥ 2 × ULN
- Total bilirubin ≥ 5 × ULN
- Total bilirubin ≥ 8 × ULN
- ALT or AST ≥ 3 × ULN and Total bilirubin ≥ 2 × ULN
- ALP ≥ 2 × ULN and (baseline ALP < 2 × ULN or baseline ALP missing)
- Direct bilirubin ≥ 2 × ULN
- Direct bilirubin ≥ 5 × ULN

- GGT ≥ 2 × ULN
- ALT ≥ 3 × ULN and INR ≥ 1.5
- ALP ≥ 2 × ULN
- ALP ≥ 3× ULN
- INR ≥ 1.5 × ULN
- INR ≥ 3 × ULN
- INR ≥ 5 × ULN

The number and percent of patients falling in each of the following categories based on confirmed results after first dose will be tabulated by treatment group (a confirmed value is based on a consecutive lab value performed on a different day to, but within 10 days of, the initial value. If that value is in the same or worse category then the initial value is confirmed. If the consecutive value is in a better category then the initial value is confirmed using the consecutive value category. If there is no retest within 10 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 × ULN or ALT/AST ≥ 2 × Baseline, which is confirmed
- ALT/AST ≥ 3 × ULN, which is confirmed
- ALT/AST ≥5 × ULN, which is confirmed
- ALT/AST ≥10 × ULN, which is confirmed
- ALT/AST ≥20 × ULN, which is confirmed

For patients having at least 3-fold or greater elevations above the ULN for ALT or AST or for patients with baseline ALT or AST ≥ ULN at least 2-fold increases from Baseline, spaghetti plots and a listing of all of the ALT, AST, total bilirubin, direct bilirubin, INR, and ALP records will be provided.

For patients having elevation in liver enzymes (ALT ≥ 3 × ULN), the time to onset of the first event will be summarized using descriptive statistics

Other liver abnormalities including elevation of ALT (≥ 3 × ULN) accompanied by INR ≥ 1.5, elevation of ALT (≥ 3 × ULN) accompanied by elevated total bilirubin ≥ 2 × ULN and ALP ≥ 2 × ULN will be reviewed by the study team and summarized if needed.

Additionally, evaluation of Drug Induced Serious Hepatoxicity (eDISH) plots by treatment group will be provided for liver safety parameters (AST, ALT, Total bilirubin and ALP).

Renal Laboratory Abnormalities:

The number and percent of patients falling in each of the following categories based on results at a) any time after first dose) and b) the final visit will be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided.

- Serum creatinine ≥ 0.3 mg/dL higher than baseline
- Serum creatinine ≥ 50% higher than baseline

A listing of the creatinine values over time will be provided for each patient meeting either of the two criteria.

The number and percent of patients falling in each of the following additional categories based on results at any time after first dose will also be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided.

- Serum creatinine ≥ 2.0 × baseline, and ≥ 3.0 × baseline
- eGFR reduction from baseline, ≥ 25%, ≥ 30% , ≥ 50%, and ≥ 75%
- UACR ≥ 300 mg/g, ≥ 500 mg/g, ≥ 600 mg/g, ≥ 1200 mg/g
- UACR increase from Baseline ≥ 50%
- UPCR ≥ 500mg/g, ≥ 1000 mg/g, ≥ 2000 mg/g

A listing of creatinine and eGFR will be provided for those patients having ≥ 2-fold elevation above baseline in creatinine or ≥ 50% decrease from baseline in eGFR.

For patients having eGFR ≥ 25% decrease from baseline, the time to onset of the first event will be summarized using descriptive statistics.

Platelet Abnormalities:

The incidence of patients with post-baseline platelets results falling in each of the following categories will be summarized for the Safety Set and the subset of patients with normal baseline (≥ 140,000/mm^3). The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided for selected categories.

- 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 platelet count falling in: ≥ 140,000/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, 0 to < 25,000/mm^3 (the risk difference will not be provided for this category)
- Worst platelet reduction from Baseline ≥ 30% and ≥ 50%

The incidence of patients with post-baseline platelets results falling in each of the following categories based on confirmed results will also be summarized:

- Worst platelet count falling in: ≥ 140,000/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, 0 to < 25,000/mm^3 (the risk difference will not be provided for this category)
- Worst platelet reduction from Baseline ≥ 30% and ≥ 50%

For patients having post-baseline platelet count < 100,000/mm^3, the time to onset of the first event will be summarized using descriptive statistics

The correlation between anti-platelet antibodies and platelet decrease as well as immunogenicity status may be explored if supported by data.

Hypersensitivity Related Analyte Abnormalities:

The number and percentage of patients falling in each abnormality category outlined below will be tabulated by treatment group. The risk different (95% CI) in the crude incidence rates between each active treatment group (or total ISIS 678354) and pooled placebo group will be provided for selected categories.

- Eosinophils > 650 cells/uL, > 1500 cells/uL, > 5000 cells/uL
- WBC > 10,800 cells/uL, > 13,000 cells/uL, > 15,000 cells/uL

Shift Analysis

The following hematology and hepatic enzymes lab results will be categorized 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 Baseline to worst post-baseline value taken after the first dose will be summarized. If a patient is missing a baseline value but has a post-baseline value, then the baseline assessment will be labelled as "unknown". Likewise, if a patient has a baseline value but has no post-baseline values, then the worst value will be labelled as "unknown". Number and proportion of patients with shift from baseline to worst post-baseline values based on the confirmed results by toxicity category for ALT, AST, and platelets will also be tabulated.

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

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

Shift from Baseline to maximum post-baseline value for urinary albumin/creatinine ratio, protein/creatinine ratio and LDL-C by treatment group will be provided. The categories for the shift table will be:

- Urinary albumin/creatinine ratio: < 30 mg/g; 30 to < 300 mg/g; ≥ 300 mg/g
- Urinary protein/creatinine ratio: < 150 mg/g; 150 to < 500 mg/g; 500 to < 1000 mg/g; ≥ 1000 mg/g
- LDL-C: < 70 mg/dL, 70 to < 100 mg/dL, 100 to < 130 mg/dL, 130 to < 160 mg/dL, 160 to < 190 mg/dL and ≥ 190 mg/dL.

4.10.6. Vital Signs and Physical Findings

Vital signs include:

- pulse rate (beats/minute)
- systolic and diastolic blood pressure (SBP and DBP) (mmHg)
- respiration rate (breaths/min)
- body temperature, measured under the arm pit (°C)
- weight
- BMI

Summary tables will be created to present the descriptive statistics for vital sign values as well as the change and percent change from Baseline at each study visit.

Number and percentage of subjects falling in each of the following categories will be tabulated by treatment group:

- Change from baseline in SBP > 5, > 10, > 15, > 20, > 30 mmHg
- Change from baseline in DBP > 5, > 10, > 15, > 20, > 30 mmHg
- Change from baseline in pulse > 5, > 10, > 15, > 20 bpm

A by-subject listing of vital signs will be provided.

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

4.10.7. 12-Lead Electrocardiograms (ECG)

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, QTc intervals (machine reading), QTc interval calculated using Fridericia's formula (QTcF) and overall interpretation. For the continuous variables above, descriptive statistics of the average of triplicate results at each study visit, as well as the change and percent change from Baseline to each study visit, will be presented in summary tables; for the categorical responses to overall interpretation, the worst of triplicate results at each visit will be summarized by counts and percentages. All the data collected in triplicate will be listed. Following summary tables will be presented.

- A summary of each ECG parameter by treatment group and visit
- A summary of the number and percentage of subjects with QTcF interval exceeding the following predefined upper limit: > 450 ms, > 480 ms, > 500 ms. The average of triplicates will be used to categorize the data.
- Shift table from baseline to the worst (highest) post-baseline QTcF interval by treatment group. The categories for the shift table will be: ≤ 450 msec, > 450 msec to ≤ 480 msec, > 480 msec to ≤ 500 msec, and > 500 msec. The average of triplicates will be used to categorize the data.

- The number and percent of patients experiencing an increase from baseline in QTcF interval of greater than 30 msec or 60 msec at any time post-baseline will be summarized by treatment group. This analysis will be presented for all patients in the Safety set and also for the subgroup whose QTcF is normal at baseline. Normal QTcF is defined as ≤ 450 msec for males or ≤ 470 msec for females. The average of triplicates will be used to determine the increase.

ECG results will be listed.

4.10.8. Data and Safety Monitoring Board (DSMB)

A DSMB, also known as Data Monitoring Committee, will be assembled to review safety and tolerability data collected during this study. Based on its ongoing assessment of the safety and tolerability, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the DSMB Charter.

4.11. Other Analyses

4.11.1. Pharmacokinetics

During the treatment period, blood samples for the determination of plasma ISIS 678354 concentrations will be collected from all patients prior to dosing.

Table 2: Plasma Trough and Post-Treatment Sampling Schedule for all Patients

	Treatment Period												**Follow-up Period**		
Study Week	**1**	**3**	**5**	**9**	**13**	**17**	**21**	**25/ET-L2***	**29**	**37**	**45**	**53/ET-L5* or Tx ET**	**4****	**8****	**13/Post Tx ET****
Study Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**253**	**309**	**365**	**28****	**56****	**91****
	Pre-dose, 2 hr ± 15 min***, and 4 hr ± 30 min***	Any time	Pre-dose	Pre-dose	Pre-dose and 2 hr ± 15 min	Pre-dose	Pre-dose	Pre-dose and 2 hr ± 15 min	Pre-dose	Pre-dose	Pre-dose	Any time	Any time	Any time	Any time

* Landmark visit. For early termination landmark (ET-L) visits: Week 25 is ET-L2 and Week 53 is ET-L5
** Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval post-last dose
*** Samples can be collected within the ± 15 min and ± 30 min window, but the actual sampling time should be recorded accurately in eCRF

Plasma concentrations of ISIS 678354 (measured as total full-length oligonucleotides or ISIS 678354-eq, i.e., ISIS 678354-eq, including fully conjugated, partially conjugated, and unconjugated ISIS 678354), along with the scheduled (nominal) and actual sampling times (i.e., time from subcutaneous [SC] dosing) will be listed (when applicable) for each evaluable patient by treatment, actual dose, gender, subject ID, subject immunogenicity (IM) status and study day. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "BLQ". In addition, percent differences between scheduled and actual sampling times will also be listed.

For all patients who receive ISIS 678354 treatment, ISIS 678354 plasma trough (pre-dose), peak (2 hr and 4 hr), and post-treatment (28, 56, 84, and 119 days after the last dose) concentrations will be summarized using descriptive statistics by treatment, dose, study day, and scheduled time point, with and without stratification by IM status (see Section 4.11.2). For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum and

maximum) 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, as well as geometric mean and geometric %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 (percent difference between scheduled and actual sampling time greater than 30%), or large deviations between actual dose and nominal dose (percent difference between nominal and actual dose greater than 30%). Any samples excluded from the summary descriptive statistics, if deemed necessary, will be listed separately along with the reason for exclusion.

For patients who receive ISIS 678354 treatment and not participating in the OLE, the plasma disposition half-life associated with the apparent terminal elimination phase will be calculated using a non-compartment method, if appropriate, using available data. 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 (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by treatment and dose with and without stratification by IM status (see Section 4.11.2).

Population pharmacokinetics and covariate analysis may be performed, combined with data from other studies if deemed appropriate, and results, if generated, will be reported separately. Exposure-response relationships between selected pharmacokinetic and efficacy and safety measures may also be explored, where deemed appropriate.

4.11.2. Immunogenicity Analysis

4.11.2.1. Sample Level ADA Data

Samples collected for IM assessment at baseline (Day 1 pre-dose), during treatment and post-treatment follow-up period including early termination samples will be analyzed for anti-ISIS 678354 antibodies (ADA).

An evaluable sample will be designated 'Positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'Negative'. An unevaluable sample, for example, a sample not being stored properly, or insufficient volume for analysis, will be reported as "unknown". Sample ADA results (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-ISIS-678354 antibodies) before, during, and after treatment with study drug (ISIS-678354 or placebo) (sample ADA status) will be listed by treatment, dose, and day of collection.

The sample ADA incidence (number) and incidence rate (percent) at each evaluated study time point will be determined and appropriately summarized by treatment and dose as the total number of and percentage of evaluated subjects with sample ADA negative, positive, and unknown status. Furthermore, titer over time will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range by treatment and dose.

4.11.2.2. Subject Level ADA Data

Subject ADA status overall (ADASTAT) will be defined as 'Positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods; 'Negative' status if all evaluated ADA sample results during the treatment and post-treatment evaluation periods are ADA negative and they have at least one evaluable ADA result collected post-study drug treatment. Otherwise, a study subject will be assigned 'Unknown' ADA status.

Furthermore, subjects with positive overall ADA status may be further classified into different ADA types (ADATYPE) based on their baseline ADA status and change in ADA titer post treatment as described below (Shankar *et al.* 2014):

- Treatment-Emergent ADA: subjects with either treatment-induced ADA or treatment-boosted ADA as described below:
  - Treatment-Induced ADA: ADA developed de novo (seroconversion) following study drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA, i.e., baseline negative ADA).
  - Treatment-Boosted ADA: pre-existing ADA that were boosted to a higher level following study drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a factor of 8-fold or more).
- Treatment-Unaffected ADA: pre-existing ADA that were not affected (boosted) following study drug administration (i.e., any time after the initial drug administration the ADA titer is 4-fold or less).
- For patients with negative overall ADA status, ADATYPE would be classified as baseline negative or baseline positive, based on their baseline ADA status.

Other subject level IM parameters to be calculated/defined may include but not limited to:

- ADA category (ADACAT) will include subjects with Negative, Treatment-Unaffected, and Treatment-Emergent ADA status as described above.
- Subject ADA Status at Baseline (ADASTATB): "Positive" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed positive; "Negative" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as negative; "Unknown" if the subject has Week 1 Day 1 pre-dose sample (baseline) unevaluable.
- First day of ADA detected (TFSTADA): i.e., the first day positive ADA sample was observed, will be calculated by: the date of first sample has “positive” sample IM status - first dose date +1.
- Onset of treatment-emergent ADA (ONSETTE): i.e., the first day treatment-emergent ADA positive sample observed, and will be calculated for subjects with treatment-induced ADA and treatment-boosted ADA by:
  - For treatment-induced ADA: the date of first sample has “positive” sample IM status - first dose date +1.
  - For treatment-boosted ADA: the date of the first sample has ADA titer greater than the baseline titer by a factor of 8-fold or more – first dose date +1.
- Last Positive ADA Study Day (TLSTADA): defined as the last positive ADA sample observed from the start of study drug treatment and will be calculated by: the date of last sample has “positive” sample IM status - first dose date +1.
- Last IM Sampling Study Day (TLSTSAMP): defined as the last ADA sample collected from the start of study drug treatment and will be calculated by: the date of last sample colleted - first dose date +1.

- Duration of treatment-emergent ADA (DURTE): i.e., the total duration of treatment-emergent ADA during the study, and will be calculated using the last sample result carried forward. This parameter will be calculated for patients with treatment-induced ADA and treatment-boosted ADA.
- Peak titer (PEAKTIT): the highest titer observed for the subject.
- Time to peak titer (TPEAKTIT): the time to reach peak titer will be calculated by: the date of first peak titer observed - first dose date +1.
- Total number of ADA Positive Samples (NOPOSAMP): the total number of ADA samples being confirmed positive for the subject.
- Total number of ADA Samples evaluated (NOADASAMT): the total number of ADA samples being collected and analyzed successfully with reportable results for the subject.

Lastly, subjects with positive ADA status may further be classified as being transient or persistent ADA response, if there are sufficient number of subjects with transient ADA status. Transient and persistent ADA definitions are defined below and based on (Shankar *et al.* 2014):

Transient ADA response:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which will be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

Persistent ADA response:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The subject level ADA prevalence, incidence, and positive ADA response being transient or persistent (if applicable) will be calculated as the total number of and percentage of evaluated patients with IM negative, positive, and unknown status by treatment and dose. Subject level IM parameters (as described above), if applicable, will be listed by treatment and dose for all evaluable subjects, and also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%) and range, by treatment and dose.

4.11.2.3. Evaluation of IM Impact on PK, PD, efficacy and Safety

The impact of IM on PK, PD, and safety will be evaluated by stratifying plasma PK exposure measures (such as plasma peak, trough and post-treatment ISIS 678354 concentrations, etc.), PD biomarker levels, selected clinical efficacy end points and safety measures by subject level ADA data, summarized using typical descriptive statistics, and presented graphically and/or in tables.

Efficacy measures to be stratified by subject level ADA data (e.g., ADACAT) will include but may not be limited to apoC-III and TG levels. Safety measures to be stratified by subject level ADA data will include but may not be limited to AEs, and lab tests for hematology, liver and kidney functions, as appropriate.

Additionally, within subject comparisons on plasma C_{2h} may be conducted in patients with multiple C_{2h} concentrations and presented graphically by subject IM status overall and treatment if deemed appropriate (Wang *et al.* 2016)

Lastly, other stratifications (e.g., based on antibody titer, onset of ADA, subject ADA status at baseline, etc.) of selected PK, efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.

4.11.3. Additional/Exploratory Analysis

4.11.3.1. Percent Change in Fasting TG, apoC-III, apoB-48, and non-HDL-C at Month 3

The following tertiary/exploratory endpoints will be compared between ISIS 678354 treatment group (ISIS 678354 80 mg, ISIS 678354 50 mg) and placebo using an ANCOVA model with the percent change in original scale as the dependent variable, two stratification factors and treatment group as factors, the corresponding log-transformed baseline fasting results as covariates in the FAS. The same multiple imputation method as the primary analysis of the primary endpoint will be used for imputing missing data.

- Percent change in fasting TG from Baseline at Month 3
- Percent change in fasting apoC-III from Baseline at Month 3
- Percent change in fasting apoB-48 from Baseline at Month 3
- Percent change in fasting non-HDL-C from Baseline at Month 3

The change and percent change from Baseline in fasting TG, apoC-III, apoB-48, and non-HDL-C will be summarized by treatment group over time.

4.11.3.2. Treatment Response Rate

The following treatment response rates between ISIS 678354 treatment group (ISIS 678354 80 mg, ISIS 678354 50 mg) and placebo groups will be compared as exploratory analyses using logistic regression with the treatment group, two randomization stratification factors as the factors, and nature log-transformed baseline fasting TG as a covariate in the FAS.

- Proportion of patients who achieve fasting TG $\geq$ 40% Reduction from Baseline at Months 3 and 12
- Proportion of patients who achieve fasting TG $\geq$ 70% Reduction from Baseline at Months 3 and 12
- Proportion of patients who achieve fasting TG $\leq$ 880 mg/dL at Months 3 and 12 in the subset of FAS with baseline fasting TG > 880 mg/dL
- Proportion of patients who achieve fasting TG $\leq$ 500 mg/dL at Months 3 and 12 in the subset of FAS with baseline fasting TG > 500 mg/dL

Missing values will be handled using the same multiple imputation method as the primary analysis of the primary endpoint.

4.11.3.3. FCS Symptoms

The FCS Symptoms Questionnaire includes 4 items addressing the severity of abdominal pain, physical fatigue, difficulty thinking and diarrhea. These 4 items are administered on a daily basis and ask patients to rate the worst severity of each symptom in the past 24 hours using a 0–10 numeric rating scale. Higher scores denote more severe symptoms.

The daily symptom composite score will be calculated as the average of the non-missing scores across the 4 symptom items. If two or more questions are missing, the symptom composite score will be considered as missing for the day. If one item is missing, then the composite score will be calculated as the average of the 3 non-missing item scores

The data will be mapped to study week based on the visit window specified in Section 4.2.4. The data in the visit window will be averaged and used for summary and analysis. In addition to the weekly average, the highest (worst) response in each week will also be determined and used for summary and analysis. If patients complete less than 4 daily assessments in a week, then the weekly FCS symptom scores will be considered as missing for the week.

Item-level scores and the symptom composite scores, as well as their changes from baseline will be summarized by treatment group and by study week over time using descriptive statistics.

A summary of abdominal pain using the following categories will also be provided: no pain (pain score: 0), mild (pain score: > 0 – 3), moderate (pain score: > 3–6), or severe (pain score: > 6-10). The frequency and percentage in each category will be tabulated by treatment group and by study week over time.

The change from baseline in the weekly average item and composite scores at the primary analysis time point (average of Weeks 23 to 27) and at Month 12 (average of Weeks 49 to 53) as well as change from baseline in the highest (worst) item and composite scores at the primary analysis time point (worst of Weeks 23 to 27) and at Month 12 (worst of Weeks 49 to 53) will be analyzed using an ANCOVA model with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate, and will be conducted in the FAS.

The analyses described above will also be repeated using the corresponding FCS symptom collected at the two-week recall administered the first day of screening as the baseline.

The following two exploratory analyses will be performed in the subset of FAS patients who reported any abdominal pain (pain score > 0) at Baseline:

1. The first exploratory analysis will be performed to compare the change from Baseline in the weekly average abdominal pain scores at the primary analysis time point (average of Weeks 23 to 27) and at Month 12 (average of Weeks 49 to 53) between the ISIS 678354 treatment groups and placebo group in this subset of patients using an ANCOVA model with the two stratification factors and treatment group as the factors and baseline average abdominal pain score as covariate.
2. The secondary exploratory analysis will be performed to compare the change from Baseline in the highest (worst) abdominal pain score at the primary analysis time point (Weeks 23 to 27) and at Month 12 (Weeks 49 to 53) using an ANCOVA model with the two stratification factors and treatment group as factors and worst baseline abdominal pain score as covariate in this subset.

In addition to the analyses described above based on the observed data, the missing values will be imputed. The change from baseline in the weekly average item and composite scores at the primary

analysis time point and at Month 12 as well as change from baseline in the highest (worst) item and composite scores at the primary analysis time point and at Month 12 will be analyzed based on the imputed data using an ANCOVA model with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate, and will be conducted in the FAS.

The missing values will be imputed as follows:

- For patients with a missing baseline value, their baseline scores will be imputed using the average of non-missing data from other patients in the same stratification category. There are 4 stratification categories:
  - history of pancreatitis = Yes, previous treatment with Volanesorsen = No
  - history of pancreatitis = Yes, previous treatment with Volanesorsen = Yes
  - history of pancreatitis = No, previous treatment with Volanesorsen = No
  - history of pancreatitis = No, previous treatment with Volanesorsen = Yes

In the event of no observed data for imputation, history of pancreatitis will be used as the only classification factor for the purpose of identifying non-missing data for imputation. Additional factors, such as age and gender may be considered to further classify the imputation categories if supported by data.

The item and composite scores will be imputed separately

- The Month 6 (primary analysis time point) score will be calculated from the non-missing weekly scores from Weeks 23 to 27 and the Month 12 score will be calculated from the non-missing weekly scores from Weeks 49 to 53. If all weekly scores during the period are missing, the missing score at the primary analysis time point will be imputed using the data from the week that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ± 30 days window. If 2 or more visits with equal distance, then the average or worst will be used. The item and composite scores will be imputed separately.

The tables below list the summaries and analyses to be performed for the FCS symptom item and composite scores

Observed Data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Average FCS Symptom – item score and composite score	Baseline is defined as the average during the screening period and up to Day 1. If all assessments during the period are missing, the baseline will be considered as missing	Weekly average. If a patient has less than 4 assessments in a week, the weekly score will be considered as missing	1. Descriptive statistics of score, change and percent change over time in the FAS 2. Frequency of patients by abdominal pain category (no pain, mild, moderate and severe) over time in the FAS
		Month 6 (Primary analysis time point) - average of Weeks 23 to 27 Month 12 -average of Weeks 49 to 53	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors, and the corresponding baseline score as a covariate in the FAS 3. Descriptive statistics of abdominal pain score, change and percent change at Month 6 and Month 12 in the subset of FAS patients who reported any abdominal pain (pain score > 0) at Baseline 4. ANCOVA model of change from baseline in abdominal pain score with the two stratification factors and treatment group as factors and the baseline score as a covariate in the subset of FAS patients who reported any abdominal pain (pain score > 0) at Baseline
	Baseline is defined as the single observation collected at the first day of screening with a two-week recall	Weekly average. If a patient has less than 4 assessments within a week, the weekly score will be considered as missing	Descriptive statistics of score, change and percent change over time in the FAS

Observed Data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Average FCS Symptom – item score and composite score (Continued	Baseline is defined as the single observation collected at the first day of screening with a two-week recall (Continued)	Month 6 (Primary analysis time point) - average of Weeks 23 to 27 Month 12 -average of Weeks 49 to 53	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS
Worst FCS Symptom – item score and composite score	Baseline is defined as the worst during the screening period and up to Day 1. If all assessments during the period are missing, the baseline will be considered as missing	Weekly worst. If a patient has less than 4 assessments in a week, the weekly score will be considered as missing	1. Descriptive statistics of score, change and percent change over time in the FAS 2. Frequency of patients by abdominal pain category (no pain, mild, moderate and severe) over time in the FAS
		Month 6 (Primary analysis time point) - worst of Weeks 23 to 27 Month 12 -worst of Weeks 49 to 53	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate on FAS 3. Descriptive statistics of abdominal pain score, change and percent change at Month 6 and Month 12 in the subset of ITT patients who reported any abdominal pain (pain score > 0) at Baseline 4. ANCOVA model of change from baseline in abdominal pain score with the two stratification factors and treatment group as factors and the baseline score as a covariate in the subset of ITT patients who reported any abdominal pain (pain score > 0) at Baseline

Observed Data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Worst FCS Symptom – each item score and composite score (Continued	Baseline is defined as the single observation collected at the first day of screening with a two-week recall	Weekly worst. If a patient has less than 4 assessments in a week, the weekly score will be considered as missing	Descriptive statistics of score, change and percent change over time in the FAS
		Month 6 (Primary analysis time po–nt) - worst of Weeks 23 to 27 Month 12 -worst of Weeks 49 to 53	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

Imputed Data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Average FCS Symptom – item score and composite score	Baseline is defined as the average during the screening period and up to Day 1. If all assessments during the period are missing, the baseline will be considered as missing. Missing baseline will be imputed using the average of non-missing data from other patients in the same stratification category	Month 6 (Primary analysis time point) - average of Weeks 23 to 27 Month 12 -average of Weeks 49 to 53. If all weekly scores during the period are missing, the missing Month 6 score will be imputed using the data from the week that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ± 30 days window. If 2 or more visits with equal distance, then the average will be used.	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

Imputed Data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Average FCS Symptom – item score and composite score (Continued)	Baseline is defined as the single observation collected at the first day of screening with a two-week recall Missing baseline will be imputed using the average of non-missing data from other patients in the same stratification category	Month 6 (Primary analysis time point) - average of Weeks 23 to 27 Month 12 -average of Weeks 49 to 53. If all weekly scores during the period are missing, the missing Month 6 score will be imputed using the data from the week that is the closest to Day 169 and within a ±30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ±30 days window. If 2 or more visits with equal distance, then the average will be used.	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS
Worst FCS Symptom – each item score and composite score	Baseline is defined as the worst during the screening period and up to Day 1. If all assessments during the period are missing, the baseline will be considered as missing Missing baseline will be imputed using the average of non-missing data from other patients in the same stratification category	Month 6 (Primary analysis time point) - worst of Weeks 23 to 27 Month 12 -worst of Weeks 49 to 53 If all weekly scores during the period are missing, the missing Month 6 score will be imputed using the data from the week that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ± 30 days window. If 2 or more visits with equal distance, then the worst will be used.	1. Descriptive statistics of score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

4.11.3.4. FCS impacts

The FCS Impacts Questionnaire includes 13 items addressing potential impacts of FCS on patient functioning. These 13 items ask patients to rate the frequency of each impact in the past 7 days during the screening period and at each study visit using the following scale: Never = 0, Rarely = 1, Sometimes = 2, Often = 3, and Always = 4. Higher scores denote more severe impacts.

An impacts composite score will be calculated as the average of the non-missing scores across the 13 impact individual items. If more than 50% of the questions are missing, the impacts composite score will be considered as missing for the visit.

Item-level scores, impacts composite score and their changes from baseline will be summarized by treatment group over time using descriptive statistics.

The change from baseline in the impacts composite scores at the primary analysis time point (average of Weeks 23, 25 27) and at Month 12 (average of Weeks 49, 51 and 53) will be analyzed using an ANCOVA model with the two randomization stratification factors and treatment group as factors and baseline score as a covariate, and will be conducted in the FAS.

In addition to the analyses described above based on the observed data, the missing values will be imputed. The change from baseline in the impacts composite scores at the primary analysis time point and at Month 12 based on the imputed data will be analyzed using an ANCOVA model with the two randomization stratification factors and treatment group as factors and baseline score as a covariate, and will be conducted in the FAS.

The missing values will be imputed as follows:

- For patients with a missing baseline value, their baseline score will be imputed using the average of non-missing data from other patients in the same stratification category. In the event of no observed data for imputation, history of pancreatitis will be used as the only classification factor for the purpose of identifying non-missing data for imputation. Additional factors, such as age and gender may be considered to further classify the imputation categories if supported by data.
- The Month 6 (primary analysis time point) score will be calculated from the non-missing scores from Weeks 23, 25 and 27 and the Month 12 score will be calculated from the non-missing scores from Weeks 49, 51 and 53. If all weekly scores during the period are missing, the missing Month 6 score will be imputed using the data from the week that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ± 30 days window. If 2 or more visits with equal distance, then the average will be used.

The tables below list the summaries and analyses to be performed for the FCS impact score

Observed data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
FCS Impacts – item score and composite score	Baseline is defined as the last non-missing assessment on or prior to the Day 1	If data is not available in a visit, the score will be considered as missing	Descriptive statistics of score, change and percent change over time in the FAS
		Month 6 (Primary analysis time point) - average of Weeks 23, 25, 27 Month 12 -average of Weeks 49, 51 and 53	1. Descriptive statistics of the impacts composite score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline in the impact composite score with the two stratification factors and treatment group as factors and the baseline score as a covariate in the FAS

Imputed data			
Endpoint	**Baseline**	**Post baseline**	**Analysis**
FCS Impacts – composite score	Baseline is defined as the last non-missing assessment on or prior to the Day 1. If all pre-dose composite scores are missing, the baseline composite score will be considered as missing. Missing baseline will be imputed using the average of non-missing data from other patients in the same stratification category	Month 6 (Primary analysis time point) – average of Weeks 23, 25, 27 Month 12 -average of Weeks 49, 51 and 53 If all composite scores during the period are missing, the missing Month 6 score will be imputed using the data from the visit that is the closest to Day 169 and within a ±30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ±30 days window. If 2 or more visits with equal distance, then the average will be used.	1. Descriptive statistics of the impacts composite score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline in the impact composite score with the two stratification factors and treatment group as factors and the baseline score as a covariate in the FAS

4.11.3.5. PROMIS Patient Reported Outcome Assessments

- The PROMIS Pain Interference Short Form 8a contains 8 questions to assess self-reported consequences of pain on relevant aspects of patients' life over the past seven days. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The pain interference score will be calculated by summing the values of the response to each question to get a raw

score, then converting the raw score to a T-score using the PROMIS scoring manual. The T-score rescales the raw score into a standardized T-score with a mean of 50 and a SD of 10. A T-score of 50 is the average of the United States general population. Higher interference pain scores indicate a more severe impact of pain on a patient's life. If more than 50% of the questions are missing, the pain interference score will be considered as missing for the visit. If less than or equal to 50% of the questions are missing, the missing items will be imputed using the average of the non-missing items and rounded to the nearest integer.

The PROMIS 29+2 Profile v2.1 (PROPr) contains seven PROMIS domains (Physical Function, Anxiety, Depression, Fatigue, Pain Interference, Sleep Disturbance, and Ability to Participate in Social Roles and Activities), an additional pain intensity 0-10 numeric rating scale (NRS), plus two Cognitive Function Abilities items. The PROPr score will be calculated as:

- summing the values of the response to each question to get a raw total score for each domain. If more than 50% of the questions in a domain are missing, the domain score will be considered as missing for the visit. If less than or equal to 50% of the questions in a domain are missing, the missing items will be imputed using the average of the non-missing items in the same domain and rounded to the nearest integer.
- converting the raw domain scores to T-scores using the PROMIS scoring manual. A T-score of 50 is the average of the United States general population. Higher symptom scores indicate increased symptom burden and higher function scores indicate better functioning.
- converting the T-scores to theta values: theta = (T – 50)/10, applying SAS code using theta values to calculate a PROPr score. The code is named "MAUT" (Multi-Attribute Utility Theory) and is availablithub.com/janelhanmer/PROPr. The PROPr scores range from 0 (as bad as dead) to 1 (perfect or ideal health).
- The PROMIS Cognitive Function Short Form 4a contains 4 questions to assess patient-perceived cognitive deficits over the past seven days. The cognitive function score will be calculated by summing the values of the response to each question to get a raw score, then converting the raw score to a T-score using the PROMIS scoring manual. A T-score of 50 is the average of the United States general population. Higher cognitive function scores indicate better cognitive functioning. If more than 50% of the questions are missing, the cognitive function score will be considered as missing for the visit. If less than or equal to 50% of the questions are missing, the missing items will be imputed using the average of the non-missing items and rounded to the nearest integer.

The pain interference score, PROPr domain and total scores, and cognitive function score will be summarized by treatment group over time using descriptive statistics. The changes from baseline at the primary analysis time point (average of Weeks 23, 25, 27) and at Month 12 (average of Weeks 51 and 53 for PROPr domain and total scores and cognitive function scores, average of Weeks 49, 51 and 53 for pain interference) will be analyzed using an ANCOVA model with the two randomization stratification factors and treatment group as factors and the corresponding baseline score as a covariate, and will be conducted in the FAS.

In addition to the analyses described above based on the observed data, the missing values will be imputed. The changes from baseline at the primary analysis time point and at Month 12 based on the imputed data will be analyzed using an ANCOVA model with the two randomization stratification

factors and treatment group as factors and the corresponding baseline score as a covariate, and will be conducted in the FAS. The missing values will be imputed as follows:

- For patients with a missing baseline value, their baseline score will be imputed using the average of non-missing data from other patients in the same stratification category. In the event of no observed data for imputation, history of pancreatitis will be used as the only classification factor for the purpose of identifying non-missing data for imputation. Additional factors, such as age and gender may be considered to further classify the imputation categories if supported by data.
- The Month 6 (primary analysis time point) score will be calculated from the non-missing scores from Weeks 23, 25 and 27 , the Month 12 pain interference score will be calculated from the non-missing scores from Weeks 49, 51 and 53, and the Month 12 PROPr domain and total scores and cognitive function score will be calculated from the non-missing scores from Weeks 51 and 53. If all scores during the period are missing, the missing Month 6 score will be imputed using the data from the week that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 pain interference score will be imputed using the data from the week that is the closest to the Day 351 and within a ± 30 days window, the missing Month 12 PROPr domain and total scores and cognitive function score will be imputed using the data from the week that is the closest to the Day 358 and within a ± 30 days window. If 2 or more visits with equal distance, then the average will be used.

The tables below list the summaries and analyses to be performed for the PROPr domain and total scores, pain interference score, and cognitive function score

Observed data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
PROMIS 29+2 domain and total scores, cognitive function scores	Baseline is defined as the last non-missing assessment on or prior to Day 1	If data is not available in a visit, the score will be considered as missing	Descriptive statistics of domain and total scores, change and percent change over time in the FAS
		Month 6 (Primary analysis time point) - average of Weeks 23, 25, 27 Month 12 -average of Weeks 51 and 53	1. Descriptive statistics of the domain and total scores, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline in the domain and total scores with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

Observed data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Pain interference	Baseline is defined as the last non-missing assessment on or prior to Day 1	If data is not available in a visit, the score will be considered as missing	Descriptive statistics of score, change and percent change over time in the FAS
		Month 6 (Primary analysis time point) - average of Weeks 23, 25, 27 Month 12 -average of Weeks 49, 51 and 53	1. Descriptive statistics of the scores, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

Imputed data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
PROMIS 29+2 domain and total scores, cognitive function scores	Baseline is defined as the last non-missing assessment on or prior to Day 1. If all pre-dose scores are missing, the baseline score will be considered as missing. Missing baseline will be imputed using the average of non-missing data from other patients in the same stratification category	Month 6 (Primary analysis time point) - average of Weeks 23, 25, 27 Month 12 -average of Weeks 51 and 53 If all scores during the period are missing, the missing Month 6 score will be imputed using the data from the visit that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 358 and within a ± 30 days window. If 2 or more visit with equal distance, then the average will be used.	1. Descriptive statistics of the domain and total scores, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline in the domain and total scores with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

Imputed data			
Endpoint	**Baseline**	**Post-baseline**	**Analysis**
Pain interference	Baseline is defined as the last non-missing assessment on or prior to Day 1. If all pre-dose composite scores are missing, the baseline composite score will be considered as missing. Missing baseline will be imputed using the average of non-missing data from other patients in the same stratification category	Month 6 (Primary analysis time point) - average of Weeks 23, 25, 27 Month 12 -average of Weeks 49, 51 and 53 If all composite scores during the period are missing, the missing Month 6 score will be imputed using the data from the visit that is the closest to Day 169 and within a ± 30 days window, the missing Month 12 data will be imputed using the data from the week that is the closest to the Day 351 and within a ± 30 days window. If 2 or more visits with equal distance, then the average will be used.	1. Descriptive statistics of the score, change and percent change at Month 6 and Month 12 in the FAS 2. ANCOVA model of change from baseline with the two stratification factors and treatment group as factors and the corresponding baseline score as a covariate in the FAS

4.11.3.6. The Patient Global Impression of Severity Scale (PGIS) score and Patient Global Impression of Change (PGIC) Score

The PGIS score (scaled None = 0, Mild = 1, Moderate = 2, Severe = 3, and Very severe=4), change from baseline in PGIS, and PGIC score (scaled Much better = 1, A little better= 2, No change = 3, A little worse = 4, and Much worse =5) will be tabulated by severity or change category and by treatment group over time.

Change from baseline in PGIS at the primary time point (average at Weeks 23, 25, 27) and at Month 12 (average of Weeks 51 and 53) will be classified to 2 categories: improved (defined as change from baseline < 0) and not improved (defined as change from baseline ≥ 0). The data will be analyzed using a logistic regression model with the two randomization stratification factors and treatment group as factors and baseline PGIS score as a covariate, and will be conducted in the FAS.

PGIC score at the primary time point (average at Weeks 23, 25, 27) and at Month 12 (average of Weeks 51 and 53) will be classified to 2 categories: improved (defined as PGIC score = Much better [< 1.5] or A little better [1.5 to < 2.5]) and not improved (PGIC score = No change [2.5 to < 3.5], A little worse [3.5 to < 4.5], Much worse [≥ 4.5]) and analyzed using a logistic regression model with the two randomization stratification factors and treatment group as factors and baseline PGIS score as a covariate, and will be conducted in the FAS.

4.11.3.7. Diet Questions

Responses to daily dietary questions will be listed.

4.11.3.8. Number of ER Visits, Incidence of All-cause Hospitalization, and Number of In-patient Days

The yearly rate of ER visits, all-cause hospitalization, and in-patient days during the treatment period will be summarized using descriptive statistics. The yearly rates for each patient will be calculated as number of ER visits, incidence of all-cause hospitalization, or number of in-patient days times 365.25 divided by number of days during the treatment period.

If supported by data, the number of ER visits and incidence of all-cause hospitalization during the treatment period may be compared between pooled ISIS 678354 treatment group and placebo group using a Negative Binomial regression model in the FAS. The model will include the treatment group and the 2 stratification factors as the factors. The logarithm of time in year that each patient observed during the Treatment Period will be used as an offset variable.

The yearly rate of in-patient days may be compared between pooled ISIS 678354 treatment group and placebo group using an ANCOVA model with the treatment group and the 2 stratification factors as the factors, and will be conducted in the FAS.

4.12. Determination of Sample Size

Based upon prior clinical trial experience with FCS patients, the SD of the percent change from Baseline in TGs is approximately 46%. With 14 patients in each ISIS 678354 treatment group and 14 in the pooled placebo group, there would be a 90% power to detect a 60% difference between each ISIS 678354 treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the ISIS 678354 treatment patients and no change in the placebo patients. Approximately 60 patients will be enrolled in this trial to account for potential early dropouts and to facilitate general safety evaluation.

Eligible patients will be randomized 1:1 to Cohort A or Cohort B and each cohort further randomized 2:1 (ISIS 678354:placebo) and stratified for:

- Prior history of pancreatitis within 10 years prior to Screening* vs. no history of pancreatitis or no history within 10 years prior to Screening
- Previous treatment with volanesorsen

* History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made

4.13. Changes in the Conduct of the Study or Planned Analysis

There are no changes from the planned analysis methodology described in the protocol.

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