A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of ISIS 678354 in Patients With Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or With Severe Hypertriglyceridemia

NCT05355402

22 March 2023

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1. STUDY INFORMATION

1.1. Protocol and Protocol Amendments

The protocol was amended 2 times. The latest version of the protocol (Protocol Amendment 2) is provided along with the change summary for the revision.

Protocol Version	Date	Document Provided
Original	23 February 2022	None
Protocol Amendment 1	31 August 2022	None
Protocol Amendment 2	22 March 2023	Protocol and change summary

IONIS PHARMACEUTICALS, INC.

ISIS 678354-CS8

A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of ISIS 678354 in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or with Severe Hypertriglyceridemia

Amendment 2 – 22 March 2023

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ISIS 678354-CS8

Amendment 2

Clinical Phase: [2b]

A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of ISIS 678354 in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or with Severe Hypertriglyceridemia

Protocol History

Original Protocol: 23 February 2022

Amendment 1: 31 August 2022

Sponsor
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

PPD MD
PPD

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, 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.

Protocol Signature Page

Protocol Number:	ISIS 678354-CS8
Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of ISIS 678354 in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or with Severe Hypertriglyceridemia
Amendment:	Amendment 2
Date:	22 March 2023

I hereby acknowledge that I have read and understand the attached clinical protocol, identified above, 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 and the Declaration of Helsinki.

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)

PROTOCOL AMENDMENT

Protocol Number: ISIS 678354-CS8

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of ISIS 678354 in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or with Severe Hypertriglyceridemia

Amendment Number: 2

Amendment Date: 22 March 2023

The following modifications to Protocol ISIS 678354-CS8 Amendment 1, dated 31 August 2022, have been made. 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
Section 8.5.2 Safety Monitoring and Permanent Stopping Rules for Renal Function	Rules for interrupting, restarting and permanently stopping treatment with Study Drug were modified.	Due to the large variability of renal function tests (eGFR, UPCR, and UACR) within individuals, renal safety monitoring rules across the olezarsen program are being updated to focus on clinically significant changes in renal function. These changes are being made across all olezarsen trials and have been endorsed by the DSMB.
Section 8.5.3 Safety Monitoring Rules for Platelet Count Results	Citrate sample for PLTs was removed from the list of additional lab analyses (Platelet Panel, Table 3).	Platelet count results using citrate tubes are not as reliable as EDTA tubes and can provide artificially lower values. Use of sodium citrate samples resulted in decrease of platelet count by 36.8% to 48.5% when compared to use of EDTA in an analysis performed by Medpace Reference Laboratories.
Section 8.5.6 Safety Monitoring for Potential Hypersensitivity Reactions	Language was edited to more clearly note symptoms of a hypersensitivity reaction and that they should be managed per standard of care	To provide clearer language regarding safety monitoring

Protocol Section	**Description of Change**	**Rationale**
Section 8.7.1 Follow-up Visits for Early Termination from Treatment Period or Post Treatment Follow-up Period	Language was edited noting that patients should be encouraged to attend all remaining landmark visits	Edited for clarity to note that the intent is that patients attend all landmarks visits regardless of when they discontinued treatment
Section 9.3.4 Adverse Event of Special Interest	Information was updated noting which events are considered Adverse Events of Special Interest (AESI).	Provided for clarity and to add pre-treatment to avoid a hypersensitivity reaction as an AESI.
Section 10.3 Populations	The definition of Full Analysis Set (FAS) was updated by removing "and who have at least 1 post-baseline TG assessment".	To include all subjects who are randomized and received any dose of Study Drug in the FAS, regardless of availability of post-baseline TG assessment.

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EXECUTIVE SUMMARY

Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of Olezarsen (ISIS 678354) in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established, or at Increased Risk for), or with Severe Hypertriglyceridemia.

Phase: 2b.

Investigational Product: Olezarsen.

Population: Adult males and females with hypertriglyceridemia [fasting TG ≥ 150 mg/dL (1.69 mmol/L)] and clinical diagnosis or increased risk of atherosclerotic cardiovascular disease (ASCVD) and adult males and females with severe hypertriglyceridemia [fasting TG ≥ 500 mg/dL (5.65 mmol/L)] with or without ASCVD.

Objectives	Corresponding Endpoints
Primary: To evaluate the effect of Olezarsen on percent change in fasting triglyceride (TG) levels compared to placebo	The primary endpoint is the percent change in fasting TG from Baseline at Month 6 (average of weeks 25 and 27) compared to placebo
Secondary: To evaluate the effect of Olezarsen as compared to placebo on: • Percent change in fasting TG levels upon longer duration of treatment (1 year) • Proportion of patients who achieve different thresholds in fasting TG	• Percent change in fasting TG from Baseline at Month 12 (average of Week 51 and Week 53) compared to placebo • Proportion of patients who achieve fasting TG < 150 mg/dL (1.69 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline TG < 500 mg/dL • Proportion of patients who achieve fasting TG < 500 mg/dL (5.65 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline TG ≥ 500 mg/dL
• Percent change in fasting apolipoprotein C-III (apoC-III), very low-density lipoprotein cholesterol (VLDL-C), remnant cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apoB, low- density lipoprotein cholesterol (LDL-C), and apoA-1	• Percent change in fasting apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1 from Baseline at Month 6 and at Month 12 compared to placebo

Objectives	Corresponding Endpoints
Secondary (Continued): • Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment • Adjudicated acute pancreatitis event rate	• Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment • Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo
Exploratory: Major adverse cardiovascular events (MACE)	• Events rates of independently adjudicated major adverse cardiovascular events (MACE). • Additional analyses of MACE composite of CV death, non-fatal MI, non-fatal ischemic stroke, and arterial revascularization (coronary and non-coronary), and the triple composite of CV death, non-fatal MI, and non-fatal ischemic stroke may be performed depending on rates of MACE.
Safety and Tolerability: To evaluate safety and tolerability of olezarsen	Safety and tolerability assessments include: adverse events, vital signs and weight, physical examinations, clinical laboratory tests, ECGs, and use of concomitant medications. Safety and tolerability results in patients receiving Olezarsen will be compared with those receiving placebo
Pharmacokinetics (PK): To evaluate PK of olezarsen	Plasma trough and post-treatment concentrations of Olezarsen

Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study done in conjunction with the TIMI Study Group, an academic research organization based at Brigham and Women's Hospital and Harvard Medical School. Eligible patients will enter an approximately 4-week Screening Period (that may be extended to 8 weeks if assessments cannot be completed within the 4-week period) that includes an at least 2-week Diet/ Life-style Stabilization/Run-In Period, and an approximately 2-week Qualification Period. Following Qualification, approximately 152 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 3:1 to receive olezarsen or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of olezarsen once every 4 weeks or matching volume of placebo (0.5 mL) during Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg olezarsen once every 4 weeks or matching volume of placebo (0.8 mL) during Weeks 1-49 of the Treatment Period. The 80 mg dose (blinded olezarsen or placebo) may be adjusted to 50 mg every 4 weeks due to tolerability or safety reasons at any point during the

study following consultation with the Sponsor Medical Monitor or designee. Randomization will be stratified by Qualification fasting TG levels of <500 mg/dL vs ≥ 500 mg/dL. Following the Week 53 visit, patients will enter the 13-week Post-Treatment Follow-Up Period.
All endpoints will be evaluated after the last patient has completed the Week 53/ET Visit.

See Appendix A for a list of activities and their timing.

Inclusion/Exclusion Criteria

Key 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. Fall into at least 1 of the following groups (a or b):
   a. Hypertriglyceridemia with fasting TG ≥ 150 mg/dL (1.69 mmol/L) and < 500 mg/dL (5.65 mmol/L) with either
      - Clinical diagnosis of ASCVD defined as documented coronary artery disease (CAD), cerebrovascular disease, or peripheral artery disease (Appendix F), or
      - At increased risk for ASCVD defined as:
        - Type 2 Diabetes mellitus, or
        - Two (2) or more of the following cardiovascular (CV) risk enhancing factors:
          - Men ≥55 years of age or women ≥ 65 years of age
          - Women with a history of preeclampsia, or premature menopause (before the age of 40 years)
          - Family history of premature ASCVD (before the age of 55 years for males, or before the age of 65 years for females)
          - Current tobacco use (5 cigarettes/day or more for at least 1 year)
          - Metabolic syndrome (see Appendix F for definition)
          - Hypertension requiring antihypertensive treatment
          - Chronic kidney disease stage 3 or (eGFR 30-59 mL/min/M^2)
          - LDL-C ≥ 160 mg/dL
          - LDL-C ≥ 100 mg/dL on therapy to lower LDL-C
          - Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
          - Elevated lipoprotein (a) (≥ 50 mg/dL or 125 nmol/L)
          - Ankle brachial index < 0.9 in asymptomatic patients
          - Coronary artery calcium score ≥ 100
   b. Severe hypertriglyceridemia with fasting TG ≥ 500 mg/dL (5.65 mmol/L)

Note: TG levels must meet inclusion criteria at both the Screening Run-In Visit and the Screening Qualification Visit. If the fasting TG is below the required level at a Visit, up to 2 additional tests may be performed with the average of the tests used to consider eligibility at that Visit.

4. Patients should be on standard of care (SOC) lipid-lowering medications per local guidelines (Appendix E). Lipid-lowering medications should be optimized and stabilized for at least 4 weeks prior to Screening to minimize changes in these medications during the study. Patients taking over-the-counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand through the end of the study.

A full list of inclusion criteria is provided in Section 5.1.

Key Exclusion Criteria

1. Diabetes with any of the following:
   a. Newly diagnosed within 12 weeks of Screening
   b. HbA1c ≥ 9.5% at Screening
   c. Change in basal insulin regimen > 20% within 3 months prior to Screening
   d. For patients with type 1 diabetes: episode of diabetic ketoacidosis, or ≥ 3 episodes of severe hypoglycemia within 6 months prior to Screening
2. Acute coronary syndrome or stroke/TIA within 6 months prior to Screening
3. Major surgery, peripheral revascularization, or non-urgent percutaneous coronary intervention (PCI) within 3 months prior to Screening, or upcoming planned major surgery or major procedure (e.g., arterial revascularization) during the course of the study
4. Active pancreatitis within 4 weeks prior to Screening

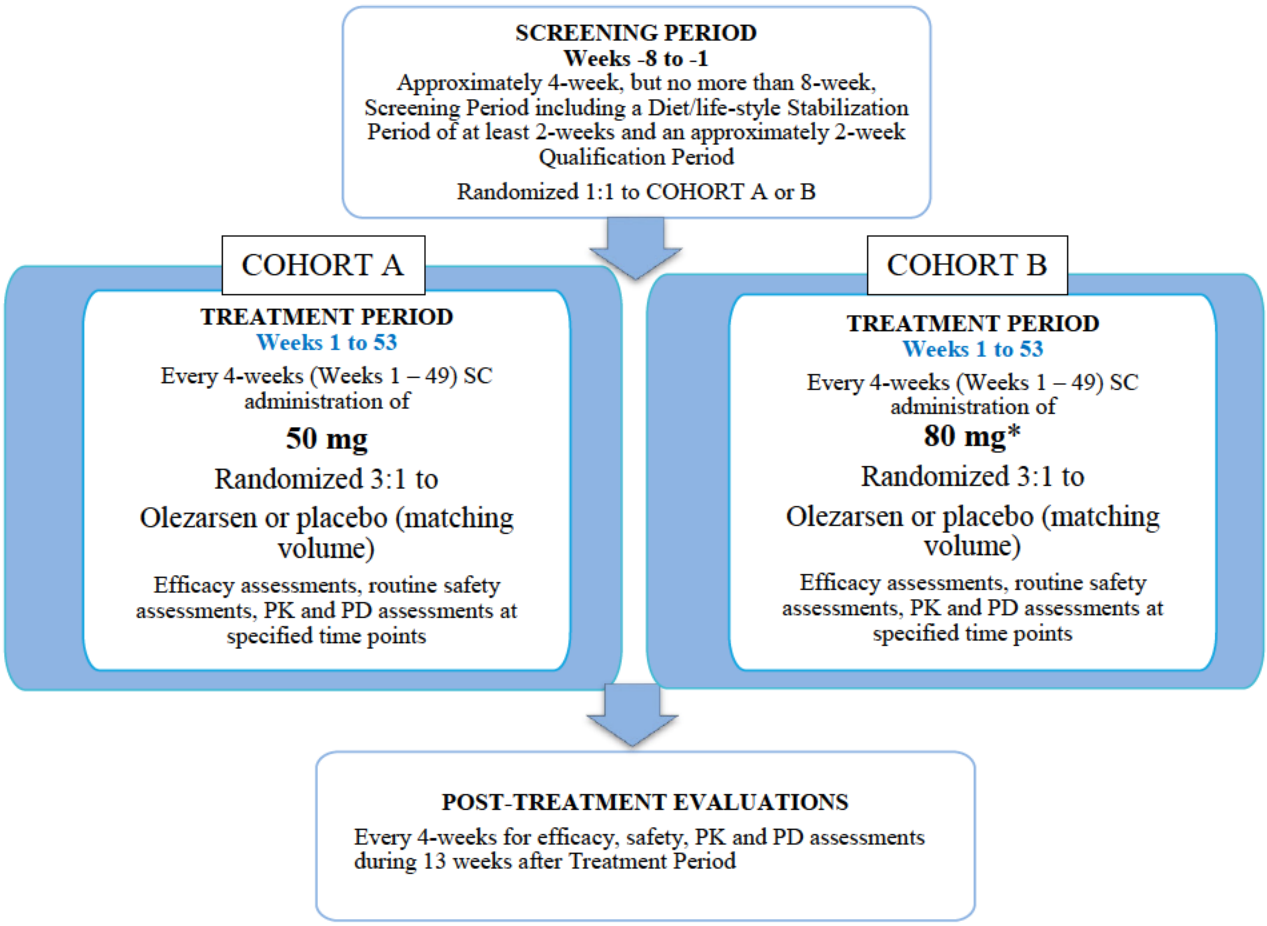
A full list of exclusion criteria is provided in Section 5.2.

Statistical Analyses:

With 33 patients in each olezarsen treatment group and 22 in the pooled placebo group, there would be an approximately 80% power to detect a 60% difference between each olezarsen treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the olezarsen treatment group, no change in the placebo patients, and a common standard deviation (SD) of approximately 73%. It is estimated that drop-out rate is approximately 20%. Approximately 152 patients will be enrolled in this trial to account for potential early dropouts and to facilitate general safety evaluations.

Additional details regarding statistical analyses are provided in Section 10.

STUDY DESIGN AND TREATMENT SCHEMA



*The 80 mg dose (blinded olezarsen or placebo) may be adjusted to 50 mg every 4 weeks due to tolerability or safety reasons at any point during the study following consultation with the Sponsor Medical Monitor or designee

STUDY GLOSSARY

Abbreviation	Definition
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
ASCVD	atherosclerotic cardiovascular disease
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CAD	coronary artery disease
CIR	copy increment from reference
CRNMB	clinically relevant non-major bleeding
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ER	emergency room
eCRF	electronic Case Report Form
eGFR	estimated GFR
FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
FSH	follicle-stimulating hormone
$GalNAc_3$	triantenary *N*-acetyl galactosamine
GCP	Good Clinical Practice
HAV	hepatitis A virus
Hb	Hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IDL	intermediate density lipoprotein
IEC/IRB	Independent Ethics Committee/ Institutional Review Board
IgM	immunoglobulin M

IM	Immunogenicity
INR	international normalized ratio
ISIS 678354	antisense inhibitor of apoC-III, olezarsen
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPL	lipoprotein lipase
MACE	major adverse cardiovascular event
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 chloesterol
NSAID	non-steroidal anti-inflammatory drug
on study	The patient is 'on study' from signing of the informed consent until their last study visit
OTC	over-the-counter
PCI	percutaneous coronary intervention
PD	pharmacodynamic(s)
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SHTG	severe hypertriglyceridemia
SOC	standard of care
Study Day 1	defined as the first day Study Drug is administered to the patient
Study Drug	olezarsen or placebo
SUSAR	suspected unexpected serious adverse reaction
TC	total cholesterol
TG	Triglyceride(s)
TRL	triglyceride-rich lipoproteins
UACR	urine albumin/creatinine ratio
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein cholesterol
VLDL-TG	very low-density lipoprotein triglyceride

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objective

To evaluate the effect of olezarsen on percent change in fasting triglyceride (TG) levels compared to placebo.

1.1.2. Secondary Objective(s)

To evaluate the effect of olezarsen as compared to placebo on:

- Percent change in fasting TG levels upon longer duration of treatment (1 year)
- Proportion of patients who achieve different thresholds in fasting TG
- Percent change in fasting apolipoprotein C-III (apoC-III), very low-density lipoprotein cholesterol (VLDL-C), remnant cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), high- density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apolipoprotein B (apoB), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A-1 (apoA-1)
- Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Adjudicated acute pancreatitis event rate

1.1.3. Exploratory Objectives

To evaluate the effect of olezarsen on MACE

1.1.4. Safety and Tolerability Objective

To evaluate safety and tolerability of olezarsen.

1.1.5. Pharmacokinetic (PK) Objective

To evaluate PK of olezarsen.

1.2. Study Endpoints

1.2.1. Primary Endpoint

Percent change in fasting TG from Baseline at Month 6 (average of weeks 25 and 27) compared to placebo.

1.2.2. Secondary Endpoint(s)

- Percent change in fasting TG from Baseline at Month 12 (average of Week 51 and Week 53) compared to placebo.

- Proportion of patients who achieve fasting TG < 150 mg/dL (1. 69 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline TG < 500 mg/dL (5.65 mmol/L).
- Proportion of patients who achieve fasting TG < 500 mg/dL (5.65 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline TG ≥ 500 mg/dL.
- Percent change in fasting apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1 from Baseline at Month 6 and at Month 12 compared to placebo.
- Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment.
- Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo.

1.2.3. Exploratory Endpoint(s)

- Events rates of independently adjudicated major adverse cardiovascular events (MACE).
- Additional analyses of MACE composite of CV death, non-fatal MI, non-fatal ischemic stroke, and arterial revascularization (coronary and non-coronary), and the triple composite of CV death, non-fatal MI, and non-fatal ischemic stroke may be performed depending on rates of MACE.

1.2.4. Safety and Tolerability Endpoints

Safety and tolerability assessments include: adverse events, vital signs and weight, physical examinations, clinical laboratory tests, electrocardiogram (ECG), and use of concomitant medications. Safety and tolerability results in patients receiving olezarsen will be compared with those receiving placebo.

1.2.5. Pharmacokinetic (PK) Endpoint(s)

Plasma trough and post-treatment concentrations of olezarsen, and potential exposure/response relationship for apoC-III and TG.

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Elevated levels of TGs in the range of 150-500 mg/dL (1.69- 5.65 mmol/L), and triglyceride-rich lipoproteins (TRLs) are consistently associated with higher risk for atherosclerotic cardiovascular disease (ASCVD) in epidemiological, genetic and clinical studies, even in subjects with well controlled LDL-C levels (Nordestgaard and Varbo 2014; Schwartz et al. 2015; Nichols et al. 2018; Langsted et al. 2020).

Severe hypertriglyceridemia (SHTG) is characterized by extremely high serum TG (≥ 500 mg/dL, 5.65 mmol/L), with the predominant elevations of dietary-derived chylomicrons, but also with varying degrees of elevated TRLs carrying remnant cholesterol (Brahm and Hegele 2015). The etiology of SHTG is multifactorial and due to both genetic, metabolic and environmental influences (NCEP 2002; Brown et al. 2012; Dron et al. 2020).

Patients with sustained chylomicronemia have numerous medical and cognitive complications (Chait and Brunzell 1992; Gaudet et al. 2016; Brown et al. 2018), but the frequent occurrence of acute and recurrent acute pancreatitis is the major cause of morbidity and even mortality. Acute pancreatitis results from the inflammatory changes caused by excessive chylomicronemia, and can be fatal or lead to pancreatic damage (Symersky et al. 2006).

Standard therapeutic TG-lowering agents are relatively ineffective in lowering hypertriglyceridemia associated with chylomicronemia overall, and especially below a threshold above which pancreatitis occurs. This is because fibrates, fish oils and niacin predominantly lower TG levels by inhibiting very low-density lipoprotein (VLDL) output from the liver but these agents have almost no effect on chylomicron synthesis and release into the circulation, which occurs in the intestine, and/or minimal effects on clearance of chylomicrons from plasma.

In summary, in the absence of effective therapy, patients with modest elevations of TGs as well as those with SHTG are at increased risk of CV events, and acute pancreatitis, respectively, and represent populations with a major unmet medical need.

2.2. Therapeutic Rationale

Apolipoprotein C-III (apoC-III) is a component of TRLs and a key regulator of plasma TG levels by modulating TRL hepatic uptake through lipoprotein lipase (LPL)-dependent and LPL-independent mechanisms (Gaudet et al. 2015; Norata et al. 2015) (Figure 1).

ApoC-III is a potent inhibitor of LPL (Lemieux et al. 2003) and at higher concentrations also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense VLDL to intermediate density lipoprotein (IDL) and to low-density lipoprotein (LDL) (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 (Breyer et al. 1999). 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).

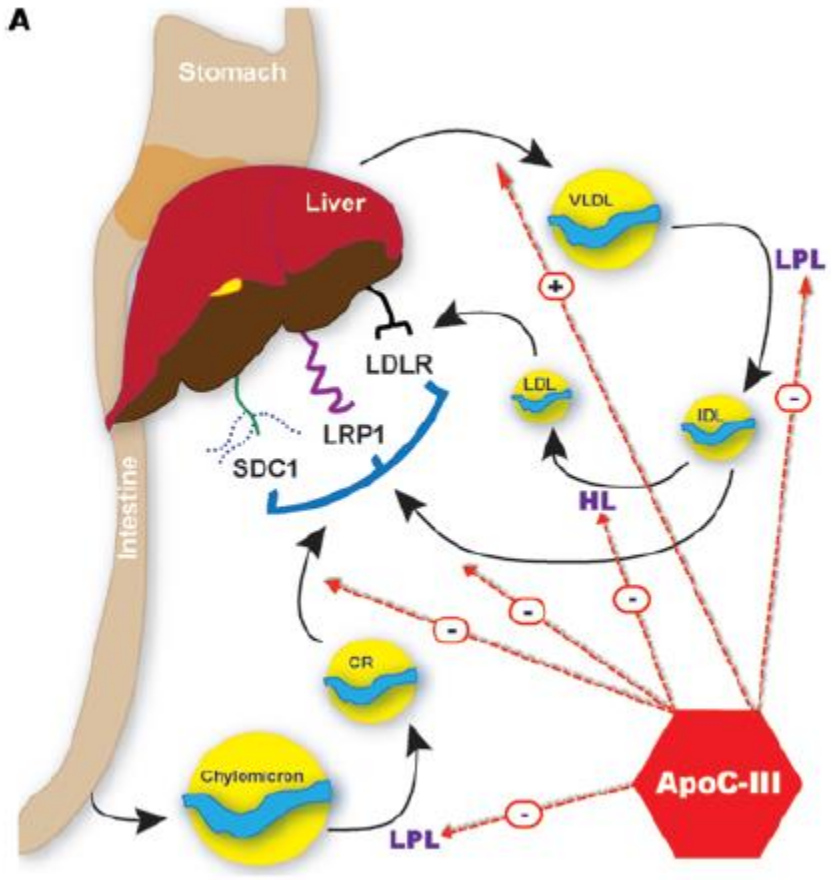


Figure 1: A Schematic Overview of the Possible Effects of ApoC-III on TRL Metabolism

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

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.

It has been suggested that apoC-III may exert proatherogenic effects directly by enhancing vessel wall inflammation and indirectly by promoting hypertriglyceridemia (Taskinen et al. 2019).

Lowering of apoC-III levels with olezarsen in clinical studies involving healthy volunteers and patients with high TGs and ASCVD demonstrated TG reduction (as described in Section 2.3.4).

2.3. Olezarsen (ISIS 678354)

Olezarsen is an antisense oligonucleotide (ASO) inhibitor of apoC-III production. Specifically, olezarsen 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 olezarsen, 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; Gaudet et al. 2015). Olezarsen, 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. Olezarsen, 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 olezarsen 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, olezarsen 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.

2.3.3 Preclinical Experience

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

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 678354 (olezarsen) can be found in the Investigator's Brochure. In addition, the results of the ISIS 678354-CS1 Phase 1 study, and Phase 2 study are provided in the respective publications (Alexander et al. 2019;

Tardif et al. 2022). A short summary of the Phase 2 study conducted with ISIS 678354 is included below.

The Phase 2 study was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. A total of 114 patients with established ASCVD, or being at risk for ASCVD, with fasting TG levels of ≥ 200 mg/dL and ≤ 500 mg/dL, and on standard-of-care preventative therapy for their known ASCVD risk factors were treated with subcutaneous (SC) injections of ISIS 678354 or matching placebo in the range of dosing equivalent to monthly drug exposure of 10 mg to 50 mg, for 6 to 12 months. Significant reductions in fasting TG levels from Baseline to the primary analysis time point at Month 6 were observed in all ISIS 678354-treated groups compared to placebo. The highest dose group (50 mg every 4 weeks) achieved mean 62% reduction from Baseline in fasting TG levels compared to placebo, associated with mean 74% reduction from Baseline in apoC-III, 57% of reduction in VLDL, and 20% reduction in non-HDL-C 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, 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 (PLT) count were observed, and no patient had a confirmed PLT count < 100,000/mm^3. 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%).

2.4 Rationale for Dose and Schedule of Administration

The 50 mg and 80 mg doses of olezarsen once every 4 weeks were chosen based on the pre-clinical data, the pharmacodynamic (PD) and safety analysis of the Phase 1 study in healthy volunteers with hypertriglyceridemia, and the results of Phase 2 study in patients with ASCVD and elevated fasting TG levels.

The highest dose that was tested in the Phase 2 study was 50 mg every 4 weeks and was found to be safe and well tolerated, however TG levels were reduced by no more than 60%. Higher doses are expected to be more effective based on the results from the Phase 1 study demonstrating dose-dependent PD effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the range of ISIS 678354 doses of 10 mg to 120 mg (per month equivalent) as compared to placebo.

Therefore, the present study will also evaluate the 80 mg dose of olezarsen that is expected to reduce fasting TG levels by more than 60% in patients with ASCVD, and to likely reduce TG levels below 880 mg/dL in substantial number of patients with SHTG, maximizing the opportunity to provide an impact on the risk of pancreatitis. Therefore, more experience with

this dose is needed. Currently 80 mg dose of olezarsen is being tested in patients with familial chylomicronemia syndrome (FCS), as well as in patients with SHTG.

2.5 Benefit-Risk Assessment

2.5.1 Overall Assessment of Benefit: Risk

The benefits of treatment of olezarsen are currently unknown. Due to its mechanism of action and based on the previous clinical experience, olezarsen has the potential to be efficacious for the treatment of patients with ASCVD or SHTG.

No specific risks have been identified with olezarsen in the Phase 1 (678354-CS1) or Phase 2 (678354-CS2) studies. The conjugated nature of olezarsen 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 safety and tolerability profile over the parent molecule, ISIS 304801.

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

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

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 olezarsen. 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 in person evaluation patients for clinical trials. In person visits should continue as planned 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 olezarsen.

3 EXPERIMENTAL PLAN

3.1 Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study done in conjunction with the TIMI Study Group, an academic research organization based at Brigham and Women's Hospital and Harvard Medical School. Eligible patients will enter an approximately 4-week Screening Period (that may be extended to 8 weeks if assessments can't be completed within the 4-week period) that includes an at least 2-week Diet/life-style Stabilization/Run-in Period, and an approximately 2-week Qualification Period. Following Qualification, approximately 152 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 3:1 to receive olezarsen or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of olezarsen once every 4 weeks or matching volume of placebo (0.5 mL) during Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg olezarsen once every 4 weeks or matching volume of placebo (0.8 mL) during Weeks 1-49 of the Treatment Period. The 80 mg dose (blinded olezarsen or placebo) may be adjusted to 50 mg every 4 weeks due to tolerability or safety reasons at any point during the study following consultation with the Sponsor Medical Monitor or designee. Randomization will be stratified by Qualification fasting TG levels of < 500 mg/dL vs. ≥ 500 mg/dL. Following the Week 53 visit, patients will enter the 13-week Post-Treatment Follow-up Period. All endpoints will be evaluated after the last patient has completed the Week 53/ET Visit.

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 or as noted for TG or apoB alerts per Section 8.5.7 of the protocol.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Approximately 152 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:

- Up to 8-week Screening Period
- A 53-week Treatment Period during which olezarsen or placebo will be administered as an every 4-week SC injection (Week 1 through Week 49)
- A 13-week Post-Treatment Follow-up Period

Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, olezarsen plasma concentrations, anti-drug antibody (ADA) testing, PLT panel, and ECGs will be performed according to the schedule of procedures in Appendix A.

3.4.1 Screening Period

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 outlined 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 Follow-up Period

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

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 experts in medical specialties relevant to the safety of ASO drugs 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 olezarsen, the DSMB will provide recommendations to the trial's Sponsor and academic leadership for modifying, stopping or continuing the study as planned. Details on the medical specialties of the members, safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and/or 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 International Conference on Harmonization (ICH), Good Clinical Practice (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 Follow-up 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 (as allowed by local regulatory authorities)**: 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, and if agreed by the patient, 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 independent ethics committee/institutional review board (IEC/IRB), as appropriate, 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 and date 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 in order to determine eligibility. However, re-screening will not be allowed if the patient screen-failed due to not meeting TG criteria. 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.

Eligible patients will enter an approximately 4-week Screening Period (that may be extended to 8 weeks if assessments can't be completed within the 4-week period) that includes an at least 2-week Diet/ life-style Stabilization/Run-in Period and a 2-week Qualification Period.

4.2 Randomization

Following Qualification, eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 3:1 to receive olezarsen or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of olezarsen once every 4 weeks or matching volume of placebo (0.5 mL) during Weeks 1–49 of the Treatment Period. Patients in Cohort B will receive 80 mg olezarsen once every 4 weeks or matching volume of placebo (0.8 mL) during Weeks 1-49 of the Treatment Period. Randomization will be stratified by Qualification fasting TG levels of < 500 mg/dL vs. ≥ 500 mg/dL.

4.3 Replacement of Patients

Patients who withdraw from the study may not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor and all patients, monitors, and Study Center personnel related to the study, (except for the DSMB and statistical/programming support staff) 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 a serious adverse event (SAE) (as defined in Section 9.3.3), and if the rare circumstance occurs where 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 Interactive Response Technology (IRT). Participant safety must always be the first consideration in making such determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor or TIMI Hotline prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. The investigator is not required to discuss un-blinding if he/she feels that emergent unblinding is necessary. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind.

The Sponsor or designee will be informed of the unblinding of a patient 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).

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. Fall into at least 1 of the following groups (a or b):
    a. Hypertriglyceridemia with fasting TG ≥ 150 mg/dL (1.69 mmol/L) and < 500 mg/dL (5.65 mmol/L) with either
        - Clinical diagnosis of ASCVD defined as documented coronary artery disease (CAD), cerebrovascular disease, or peripheral artery disease (Appendix F), or
        - At increased risk for ASCVD defined as:
            - Type 2 Diabetes mellitus, or
            - Two (2) or more of the following cardiovascular (CV) risk enhancing factors:
                - Men ≥ 55 years of age or women ≥ 65 years of age
                - Women with a history of preeclampsia, or premature menopause (before the age of 40 years)
                - Family history of premature ASCVD (before the age of 55 years for males, or before the age of 65 years for females)
                - Current tobacco use (5 cigarettes/day or more for at least 1 year)
                - Metabolic syndrome (see Appendix F for definition)

- Hypertension requiring antihypertensive treatment
- Chronic kidney disease stage 3 or (eGFR 30-59 mL/min/M^2)
- LDL-C ≥ 160 mg/dL
- LDL-C ≥ 100 mg/dL on therapy to lower LDL-C
- Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
- Elevated lipoprotein (a) (≥ 50 mg/dL or 125 nmol/L)
- Ankle brachial index < 0.9 in asymptomatic patients
- Coronary artery calcium score ≥ 100

b. Severe hypertriglyceridemia with fasting TG ≥ 500 mg/dL (5.65 mmol/L)

Note: TG levels must meet inclusion criteria at both the Screening Run-In Visit and the Screening Qualification Visit. If the fasting TG is below the required level at a Visit, up to 2 additional tests may be performed with the average of the tests used to consider eligibility at that Visit.

4. Patients should be on standard of care (SOC) lipid-lowering medications per local guidelines (Appendix E). Lipid-lowering medications should be optimized and stabilized for at least 4 weeks prior to Screening to minimize changes in these medications during the study. Patients taking over-the-counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand through the end of the study
5. Patients must be willing to comply with diet and lifestyle recommendations as able
6 Satisfy the following:
   a. Females: must be non-pregnant and non-lactating and either:
      - surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
      - 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 follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved)
      - abstinent* or
      - if engaged in sexual relations of childbearing potential, agree to use a highly effective contraceptive method from the time of signing the informed consent form until at least 30 weeks after the last dose of Study Drug (olezarsen or placebo)
   b. Males: Surgically sterile, abstinent*, or if engaged in sexual relations with a female of childbearing potential, patient is utilizing a highly effective contraceptive method from the time of signing the informed consent form until at least 30 weeks after the last dose of Study Drug (olezarsen 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.

5.2 Exclusion Criteria

1. Diabetes with any of the following:
   a. Newly diagnosed within 12 weeks of screening
   b. HbA1c ≥ 9.5% at Screening
   c. Change in basal insulin regimen > 20% within 3 months prior to Screening
   d. For patients with type 1 diabetes: episode of diabetic ketoacidosis, or ≥ 3 episodes of severe hypoglycemia within 6 months prior to Screening
2. Acute coronary syndrome or stroke/TIA within 6 months prior to Screening
3. Major surgery, peripheral revascularization, or non-urgent percutaneous coronary intervention (PCI) within 3 months prior to Screening, or upcoming planned major surgery or major procedure (e.g., arterial revascularization) during the course of the study
4. Active pancreatitis within 4 weeks prior to Screening
5. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3.0 × ULN
   b. Total bilirubin >1.5 ULN unless due to Gilbert's syndrome
   c. Estimated GFR (eGFR) < 30 mL/min/1.73 m^2 [as determined by the CKD-EPI formula for creatinine clearance; (Levey et al. 2009)]
   d. Urine protein/creatinine ratio (UPCR) ≥ 500 mg/g
6. Uncontrolled arterial hypertension (BP > 180/100 mmHg) despite antihypertensive therapy
7. Uncontrolled hypothyroidism such as those with thyroid stimulating hormone (TSH) >1.5× ULN and free thyroxine (T4) < LLN, clinical evidence of hypothyroidism, or thyroid hormone therapy that has not been stable for ≥ 4 weeks prior to Screening
8. 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
9. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B (e.g., HBsAg positive) diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology (for example, positive for Hepatitis C antibody), but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor or designee

10. Malignancy within 5 years of Screening, except for non-melanoma skin cancers, cervical *in situ* carcinoma, breast ductal carcinoma *in situ*, or stage 1 prostate carcinoma 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 or designee
11. Hypersensitivity to the active substance or to any of the excipients (olezarsen or placebo)
12. 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
13. 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
14. 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 or designee
    b. Use of bile acid resins such as colestipol, cholestyramine, or colesevelam within 4 weeks prior to Screening or planned during the study
    c. Plasma apheresis within 4 weeks prior to Screening or planned during the study
    d. Change in medications known to exacerbate hypertriglyceridemia such as certain beta blockers, thiazides, isotretinoin, oral antidiabetic medications, tamoxifen, estrogens or progestins within 4 weeks prior to Screening
    e. Change in atypical antipsychotic medications (e.g., olanzapine and clozapine) within 3 months prior to Screening
15. Blood or plasma donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening
16. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
17. Have any other conditions, including current or recent (< 1 year) alcohol abuse or other substance abuse, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or complete the study

6 STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined 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 for determination of patient eligibility after consultation with the Sponsor Medical Monitor or designee. Patients may be re-screened in order to determine eligibility. However, re-screening will not be allowed if the patient screen-failed due to not meeting TG criteria.

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 will have at least 2 weeks of Diet/life-style Stabilization/Run-in Period, followed by an approximately 2 -week Qualification Period, during which final eligibility assessments will be performed. 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 (4 weeks) post-last dose. Patients will receive Study Drug administered by SC injection once every 4 weeks during Weeks 1-49 of the 53-week Treatment Period. Collection and measurement of vital signs, physical examination results, ECGs, laboratory parameters (Appendix B), olezarsen plasma concentrations, ADA and biomarker samples, AEs and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Appendix A.

6.1.3 Post Treatment Follow-up Period

After completion of the Week 53 visit assessments, patients will enter the 13-week Post-Treatment Follow-up 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. Water and medications are not restricted during the fast, and the patient should ensure that they consume sufficient water in order to not become dehydrated.

Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status, but ideally no later than 7 days after the initial result is obtained.

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 7 days).

Hematology samples will be collected monthly during the Treatment Period, and at every visit during the Follow-up Period. In the event that a hematology sample is unreportable (e.g., due to

hemolyzed or clumped blood samples), the patient's next scheduled dose should ideally not be administered until another sample is repeated and determined not to have met a PLT count stopping rule. The Investigator or designee will contact the patient to hold dosing until a new PLT count is obtained and reviewed. Use of home care provider or local laboratory (as described below) should be considered.

Investigators may, at their discretion, test specific laboratory parameters (except for those which must remain blinded e.g., lipid panel) which may be prone to clotting, clumping or hemolysis (e.g., hematology samples) at a 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).

Blood and urine samples for renal function testing will also be collected monthly during the Treatment Period, and at every visit during the Follow-up Period, and sent to the central laboratory for analysis as per Section 8.5.2.

Liver chemistry testing will also be collected monthly during the Treatment Period, and at every visit during the Follow-up Period, and sent to the central laboratory for analysis as 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 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 PLT count results must be reviewed promptly (within 2 business days of receipt) by the Investigator, or designee, to ensure that the count has not met a dose interruption or stopping rule. Any case of PLT count reduction to levels below 50,000/mm^3 accompanied by a major bleeding (MB) event or clinically relevant non-major bleeding event (CRNMB) , or PLT 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 2 business days 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 PLT, 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 according to the Medical Data Surveillance Plan.

Further information on safety monitoring and actions to be taken by the Study Investigator are provided in Section 8.5.

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, blood pressure (BP), and pulse rate, and may also include respiratory rate and body temperature. 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 at the end of the Treatment Period (Week 53) and the end of the Post-Treatment Follow-up Period as outlined in Appendix A.

6.2.4 Pharmacokinetic Sampling

Blood samples for the determination of plasma olezarsen 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 A and Appendix C.

6.2.5 Pancreatitis Medical History

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

6.3 Requirements 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 30 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 1 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 childbearing potential uses a highly effective contraceptive method (defined below)

For female patients and female partners of male patients, highly effective 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). For female subjects in the trial, the vasectomised male partner with negative semen analysis at follow-up, should be the sole partner for that subject.

†**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 that 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. Water and medications are not restricted during the fast, and the patient should ensure that they consume sufficient water in order to not become dehydrated.

All patients will be encouraged to follow diet/life-style recommendations (Appendix E) during the study.

7 STUDY DRUG

7.1 Study Drug Description

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.

ISIS 678354 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 during 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 during 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 (ISIS 678354 or placebo) 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 and Permanent Stopping Rules

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

- For the purposes of safety monitoring and permanent stopping rules 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 initial clinical laboratory results meeting 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 of the initial collection).

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 (olezarsen 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 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 permanently stopping criteria described below are met, the patient will be permanently discontinued from further treatment with Study Drug (olezarsen or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or 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 and Permanent Stopping 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 above.

All patients will have liver chemistry tests monitored monthly during the Treatment Period. Upon completion of the study Treatment Period, liver chemistry tests should be monitored during the Post-Treatment Follow-Up Period as per visit schedule in Appendix A.

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

All lab alerts for abnormal liver chemistry tests must be promptly reviewed by the Investigator (within 2 business days of receipt) and Medical Monitor(s) according to the Medical Data Surveillance Plan.

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 (ALT/AST) and total 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), and the initial measurement(s) is confirmed (as described in Confirmation Guidance above) the following steps should be taken:

1. The Study Drug must be paused
2. Liver chemistry tests (ALT, AST, alkaline phosphatase [ALP], INR and total bilirubin) retested at least once weekly until ALT and AST levels become ≤ 1.5 × ULN or 1.5 × baseline if the baseline value was > ULN
3. Further investigations into the cause of liver chemistry elevations should be performed. These may include the following evaluations*:
    a. Obtain a more detailed history of symptoms and prior and concurrent diseases
    b. Obtain further history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
    c. Obtain a history for exposure to environmental chemical agents and travel
    d. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, cytomegalovirus (CMV) IgM, and EBV antibody panel)
    e. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA], and/ or anti-smooth muscle antibody [SMA])

*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 or designee.

4. Patients having alternative explanation for liver chemistry elevations may restart Study Drug at the original dose when ALT and AST levels become ≤ 3 × ULN (or below 2 × baseline if the baseline value was >ULN) and following consultation with the Sponsor Medical Monitor or designee who must assess that alternative etiology is well supported as the likely cause.
5. Patients without alternative explanation for liver chemistry elevations but not yet meeting permanent Stopping Rules as described in bullet #6, must have Study Drug dose permanently reduced to 50 mg, if on an 80-mg dose (blinded olezarsen or placebo). Patients treated with 50-mg dose should remain on this dose.

6. Patients without alternative explanation for liver chemistry elevations and **meeting any of the following criteria must have Study Drug stopped permanently****; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

   - ALT or AST > 8 × ULN, which is confirmed
   - ALT or AST > 5 × ULN, which is confirmed and persists for ≥ 2 weeks
   - 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
   - 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)

** The Investigator may decide to permanently stop Study Drug based on lesser changes in these parameters, taking into account all available and relevant data.

8.5.2 Safety Monitoring and Permanent Stopping Rules for Renal Function

All patients will have renal function tests monitored monthly during the Treatment Period. Upon completion of the study Treatment Period, renal function tests should be monitored during the Post-Treatment Follow-Up Period as per visit schedule in Appendix A.

Renal function surveillance will include serum creatinine and urinalysis including UACR and UPCR. The assessment of serum creatinine and urinalysis more frequently than monthly will be guided by the Sponsor Medical Monitor or designee.

All renal function test results will be reviewed on an ongoing basis at the safety review by the Sponsor Medical Monitor or designee.

All lab alerts for renal function tests must be promptly reviewed by the Investigator (within 2 business days of receipt) and Medical Monitor(s) according to the Medical Data Surveillance Plan.

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.

If any of the below criteria are met,

- eGFR (by CKD-EPI formula) decrease from Baseline > 40%
- UPCR > 1000 mg/g
- UACR > 600 mg/g

and the initial measurement(s) is confirmed (as described in Confirmation Guidance above) the following steps should be taken:

1. The Study Drug must be paused
2. Further investigations into the cause of renal function abnormalities should be performed. These may include review of patient's prior and concurrent diseases and procedures, concomitant medications for potentially nephrotoxic agents, and search for potential pre-renal causes.
3. Patients having alternative etiology identified that may account for abnormal renal results may restart treatment with Study Drug when:
   a. Lab values have improved to:
      – eGFR decrease < 40% from baseline, and/or
      – UPCR < 1000 mg/g, and/or
      – UACR < 600 mg/g, and
   b. Study Medical Monitor or designee has approved Study Drug treatment to restart
4. Patients without identified alternative etiology for renal function abnormalities may restart Study Drug Treatment when:
   a. Lab values have improved to:
      – eGFR decrease < 20% from baseline, and/or
      – UPCR < 500 mg/g, and/or
      – UACR < 300 mg/g, and
   b. Study Medical Monitor or designee has approved Study Drug treatment to restart
5. Patients without alternative explanation for renal function abnormalities and **meeting any of the following criteria must have Study Drug stopped permanently***; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:
   - eGFR (by CKD-EPI formula) decrease from Baseline >50%
   - UPCR > 2000 mg/g
   - UACR > 1200 mg/g

* The Investigator may decide to permanently stop Study Drug based on lesser changes in these parameters observed in isolation or in association with other renal-related abnormalities, taking into account all available and relevant data.

8.5.3 Safety Monitoring and Permanent Stopping for Platelet Count Results

All patients will have PLT counts monitored monthly during the Treatment Period. Upon completion of the study Treatment Period, PLTs will be monitored as per visit schedule in Appendix A.

All PLT count results must be reviewed promptly (within 2 business days 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	**Study Drug**	**Monitoring**
≥ 100K/mm^3	No action	Monitor every month
Below values to be confirmed ideally within 3 days but no later than 7 days	**If PLT count is confirmed, follow dosing guidance below[1]:**	**If PLT count is confirmed, follow monitoring guidance below[1]:**
≥ 75K to < 100K/mm^3	**Discussion with Medical Monitor**[3]	Closer observation; monitor every 2 weeks[2]
≥ 50K to < 75K/mm^3	Pause dosing. When ≥ 2 successive PLT count values return to ≥ 75K/mm^3 restart dosing **only if approved by Medical Monitor**[3]	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 Platelet panel to be drawn (Table 3)
< 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[1,4] Consider referral to hematologist Discontinue anticoagulants/antiplatelet agents/NSAIDs medication while PLT count < 50K/mm^3 if possible Platelet panel to be drawn (Table 3)

[1] Recommended if platelet count decrease / thrombocytopenia cannot be explained by other reasons and is therefore considered drug related.

[2] Once a patient commences every 2-week monitoring this frequency of monitoring should continue until the platelet count returns to ≥ 100K/mm^3 for 2 successive values.

3 The suitability of the patient for reduced (from blinded olezarsen/placebo 80 mg to 50 mg), 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.

[4] Recovery in platelet count may be accelerated by administration of high-dose glucocorticoids. Treatment as recommended by the American Society of Hematology (ASH) (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; Provan et al. 2019).

Any case of a confirmed 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 adverse event of special interest (AESI) and should be reported following the same requirements as for SAE reporting (Section 9.4.1).

The following (Table 3) is a list of lab analyses that should be performed for any patient with an occurrence of confirmed PLT count less than 50,000/mm^3 during this study. Archived samples prior to Day 1 of investigational treatment may also be analyzed in order to determine the patient's baseline conditions.

Table 3: Platelet Panel

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
EDTA sample for PLTs
To Be Performed at Central Lab
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
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies
Anti-ASO antibody

Note: In addition, these labs may also 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 and Permanent Stopping Rules 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 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 olezarsen 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 any sign or symptom of hemorrhage (e.g., more bleeding that would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for MB but does meet at least 1 of the following criteria (Kaatz et al. 2015):

1. Requiring medical intervention by a healthcare professional
2. Leading to hospitalization or increased level of care
3. Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

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

In the event of MB or CRNMB as assessed by the Investigator, and in the absence of any alternative explanation for the cause of bleeding dosing of a patient with Study Drug (olezarsen or placebo) may be interrupted or 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).

8.5.5 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 including: 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 for ADA and be discussed with the Medical

Monitor or designee to determine whether additional monitoring or laboratory tests are required. 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 Triglyceride and Apolipoprotein B Elevations

Triglycerides (TG) will be monitored for safety every 3 months. If the measured triglyceride level either (a) in patients with Baseline TGs < 500 mg/dL subsequently exceeds 880 mg/dL or (b) in patients with Baseline TGs ≥ 500 mg/dL and < 2000 mg/dL subsequently exceeds 2000 mg/dL and increases by at least 10% from Baseline or (c) in patients with Baseline TGs ≥ 2000 mg/dL subsequently increases by at least 30% from Baseline, the site will be notified to contact the patient by phone as soon as able, and no later than their next monthly visit or phone call, to counsel the patient on dietary, lifestyle and medication compliance, and educate and assess the patient for signs and symptoms of pancreatitis. To maintain the blind, the same notification will be provided for an additional patient in the other treatment group using pre-defined criteria to balance the frequency of alerts for both treatment groups, active and placebo. If the TG value remains persistently high at the next regularly scheduled TG safety assessment, a qualified individual, ideally not associated with that subject's assessment, will be informed of the TG value to evaluate and manage the patient's TG levels, moving forward throughout the study, ideally independent of the Investigator's and Study Coordinator's knowledge.

Given the potential for LPL inhibition to change the distribution of cholesterol on lipoproteins, without necessarily affecting the number of cholesterol-rich lipoproteins, apoB levels rather than LDL-C levels will be monitored for safety at 6 months then every 3 months, consistent with guidelines which recognize apoB as the optimal atherogenic lipid metric (Mach et al. 2020). If the measured apoB level increases by ≥ 20 mg/dL, the site will be notified to counsel the patient at their next monthly visit on lifestyle and medication compliance. To maintain the blind, the same reminder will be provided for an additional patient in the other treatment group, using pre-defined criteria to balance the frequency of alerts for both treatment groups, active and placebo. If the subsequent measurement is still high, then the Investigator will be informed of the apoB value and if clinically indicated based on local SOC, may adjust background lipid lowering therapy, in consultation with the patient, according to patient's ASCVD risk.

8.6 Adjustment of Dose and/or Treatment Schedule

Dose adjustments for PLT 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 or designee.

Dose adjustments should not occur unless absolutely necessary prior to Week 25.

8.7 Discontinuation of Study Drug Administration

Reasons for permanent discontinuation of Study Drug administration are:

- The patient experiences an AE that necessitates permanent discontinuation of Study Drug

  - At the discretion of the Investigator due to a safety concern
  - At the patient's request due to an adverse event
  - The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.5
  - The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- Reasons not related to an AE
  - Patient request to stop Study Drug but continue study participation
  - The patient withdraws consent for study participation
  - Investigator decision (e.g., non-compliant patient)
  - Sponsor decision

The reason for discontinuation of Study Drug must be recorded in the eCRF and source documentation. If the Investigator decides that discontinuation of Study Drug is warranted, the Investigator should make every effort to contact the Sponsor or TIMI Hotline prior to discontinuation of Study Drug.

Patients who had Study Drug administration discontinued for any reason other than full withdrawal of consent for study participation should continue their participation in the study, attending visits and procedures as per Section 8.7.1, if possible, and providing survival status by the end of the trial. If the patient declines or is unable to attend study visits, the Investigator should clarify what type of follow-up the patient is agreeable to: in person, by phone/mail, through family/friends, via correspondence/communication with other physicians, and/or from review of the medical records, and as allowed per local regulations. Wherever possible these patients should continue to be followed up via the agreed means to collect information on AE, concomitant medications and survival status. At the very least, the patient's status at the end of the Treatment Period should be ascertained and documented wherever possible. The agreed means of follow-up will be documented in the patient records and notified to the Sponsor.

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

If a patient discontinues early from the Treatment Period, treatment early termination (Tx-ET) visit assessments should be performed 4 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. Patients should also be strongly encouraged to attend remaining landmark visits at Weeks 25 and 27, as well as at 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. Depending on the day of discontinuation, follow-up visits and landmark visits may overlap and can be combined.

Any patient who chooses to discontinue early from the Post-Treatment Follow-up Period should be strongly encouraged to complete safety procedures and observations in accordance with Appendix A. If the patient declines or is unable to participate in the above, final post-treatment

early termination (Post-Tx ET) assessments should be performed at the time of withdrawal in accordance with Appendix A.

8.8 Withdrawal of Patients from the Study Procedures

A participant may withdraw from the study at any time at his/her own request. Patients should be encouraged to complete the early termination study procedures and observations at the time of withdrawal (Appendix A). 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.

Full withdrawal of consent: Any patient who provides full withdrawal of consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request.

If a participant withdraws consent from the study, he/she may request destruction of any remaining samples taken and not tested, and the Investigator must document any such requests in the site study records and notify the Sponsor accordingly.

If the participant withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. In participants who request to prematurely stop Study Drug and study-related procedures, collection of adverse events and clinical endpoints will continue as permitted by local laws and regulations, unless the participant requests otherwise.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Publicly available information should be used to determine vital status (whether the participant is alive or dead) as permitted by local law.

8.8.1 Lost to Follow-up

To prevent participants being lost to follow-up, their contact details, including next of kin contacts, should be collected initially and updated regularly by the site staff or representative. The Investigator should educate the participant on the importance of contact with the Investigator throughout the study.

Repeated attempts will be made to locate and obtain pertinent medical information for participants who are initially lost to follow-up. A participant will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study despite multiple attempts to contact him/her via telephone, fax, email, certified letter, or through patient locator agencies (if allowed by national regulation). Where permissible by local law, the Informed Consent Document will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost participants using publicly available source.

8.9 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.

8.9.1 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

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. If a disallowed concomitant therapy is administered, the study Investigator must discuss with the Medical Monitor / TIMI whether Study Drug may continue. Regardless of the decision regarding Study Drug continuation, all other study procedures and follow-up should continue as described in the protocol.

8.9.2 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.

8.10 Treatment Compliance

At each applicable dosing visit, patients may be administered study drug by a delegated study staff member. The study drug administration and compliance will be documented as per the protocol, Study Drug Manual, and captured in the electronic data capture system. If study drug is administered by a home healthcare professional, source documentation will be completed and provided to the site to document the details of study drug administration. If study drug is self-administered, after appropriate training of patient and/or caregiver, site staff will record the study drug administration details via contact with the patient.

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 Reporting Requirements

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

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) 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 (olezarsen 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 in accordance with EC Clinical trials Directive 2001/20/EC or as per national regulatory requirements in participating countries.

9.3 Definitions

9.3.1 Adverse Event

An adverse event (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 adverse event 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 ADR.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the adverse event 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 (SAE)

A SAE is any adverse event 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

  Note: 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 adverse reaction 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 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room (ER) 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 adverse event (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 adverse event 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 PLT count < 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.
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 immediately, without undue delay, but no later than 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 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 (olezarsen or placebo) is characterized by 1 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 (olezarsen 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 (olezarsen or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (olezarsen 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 - Same Dose:** Dosing and/or dosing frequency was temporarily interrupted/changed or delayed due to the AE and restarted at the same dose
- **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 Adverse Event 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 MACE will be adjudicated by a blinded, independent MACE-Adjudication Committee (MACE-AC) as outlined in the MACE Adjudication Charter.

MACE-AC will adjudicate all fatal events and events suggestive of non-fatal myocardial infarction, hospitalization for unstable angina, hospitalization for (worsening) heart failure, coronary and non-coronary revascularization procedures, and stroke. The criteria used by the MACE-AC to determine the occurrence of any of the events will follow the recommendations included in published Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (Hicks et al. 2018; Thygesen et al. 2018).

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 sheet.

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 (olezarsen or placebo) errors (for example, overdose, underdose, and administration error) should be reported as a medication error on the Protocol Deviation CRF and an AE CRF, if applicable. A brief description should be provided when reporting the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and whether the event was accidental or intentional.

Dosing details should also be captured on the Dosing Case Report Form. If the patient takes a dose of Study Drug that exceeds protocol specifications and the patient is symptomatic, then each symptom 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 adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. 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 refer to the Guidance to Investigator's section of the Investigator's Brochure and 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, or within 30 weeks of the last dose of study drug, 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 factor is:

- TG ≥ 500 mg/dL (5.65 mmol/L) vs. < 500 mg/dL at Qualification

Subgroup analysis for primary and secondary endpoints will include, but not be limited to, baseline TG ≥ 500 mg/dL vs. < 500 mg/dL, age group, race, sex, BMI, diabetes status, baseline HbA1c, use of baseline background lipid-modifying therapy versus none, statins versus no statins, previous treatment with Volanesorsen. Details of the subgroup analyses will be provided in the SAP.

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

10.2 Sample Size Considerations

With 33 patients in each olezarsen treatment group and 22 in the pooled placebo group, there would be an approximately 80% power to detect a 60% difference between each olezarsen treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the olezarsen treatment patients, no change in the placebo patients, and a common SD of approximately 73%. It is estimated that dropout rate is approximately 20%. Approximately 152 patients will be enrolled in this trial to account for potential early dropouts and to facilitate general safety evaluations.

10.3 Populations

Full Analysis Set: All patients who are randomized and received any amount of Study Drug (olezarsen 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, have a baseline fasting TG assessment, and who have no significant protocol deviations that could compromise the interpretation of efficacy. Significant deviations 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 any amount of olezarsen 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, Month 6 and Month 12

Baseline PLT is defined as the average of all non-missing pre-dose assessments.

Baseline lipid measurements are defined as the average of the pre-dose measurement on Day 1 and all measurements from the Qualification Period. If the Day 1 pre-dose and Qualification Period measurements are all missing, then the last non-missing measurement from the Screening Period will be used as baseline.

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

The Month 6 lipid assessments are defined as the average of Weeks 25 and 27 fasting assessments. The Month 12 lipid assessments are defined as the average of Weeks 51 and 53 fasting assessments. For both Month 6 and Month 12, if 1 of the 2 assessments is missing, then the non-missing assessment will be used.

10.5 Interim Analysis and Multiplicity

10.5.1 Unblinded Interim Safety Analysis

An unblinded interim safety analysis will not be conducted.

10.5.2 Multiplicity for the Final Efficacy Analysis

The multiplicity will be controlled by using a hierarchical ranking strategy in the following testing sequence. All tests will be conducted at a two-sided alpha level of 0.05. If any test is not statistically significant, the test(s) at the lower rank will be considered exploratory.

1. Primary endpoint: Comparison of percent change in fasting TG from Baseline to Month 6 between olezarsen 80-mg treatment group and pooled placebo group in the FAS
2. Primary endpoint (not co-primary endpoint): comparison of percent change in fasting TG from Baseline to Month 6 between olezarsen 50-mg treatment group and pooled placebo in the FAS.
3. Secondary endpoints: the testing sequence for the secondary endpoints will be specified in the SAP.

- Comparison of percent change in fasting TG from Baseline to Month 12 between each olezarsen treatment group and pooled placebo group in the FAS
- Comparison of proportion of patients who achieve fasting TG < 150 mg/dL (1.69 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 between each olezarsen treatment group and pooled placebo group in the subgroup of FAS with baseline TG < 500 mg/dL
- Comparison of proportion of patients who achieve fasting TG < 500 mg/dL (5.65 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 between each olezarsen treatment group and pooled placebo in the subgroup of FAS with baseline TG ≥ 500 mg/dL
- Comparison of percent change in fasting apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1 from Baseline to Month 6 and Month 12 between each olezarsen treatment group and pooled placebo group in the FAS

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.

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

Any deviation(s) from the planned analyses will be described and justified in the final clinical study report.

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 (olezarsen or placebo) received will be summarized by treatment group.

Patient incidence rates of 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 by the Medical Dictionary for Regulatory Activities (MedDRA™) system organ class, and by MedDRA™ term. A treatment-emergent AE is defined as any event not present prior to the

initiation of the Study Drug or any event already present that worsens following initiation of the Study Drug.

Tables and/or narratives of treatment emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

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 Month 6 in fasting TG between each olezarsen treatment group vs. pooled placebo group using an ANCOVA model in the FAS. The ANCOVA model will include the effects of treatment (olezarsen 80 mg, olezarsen 50 mg, or Placebo), and log-transformed baseline TG. If patients have intercurrent event(s) before Week 25, 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. The missing TG value at Months 6 or 12 will be imputed using an imputation model that contains the following variables: baseline fasting TG, fasting TG at each post-baseline visits and the multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999).

The MCMC method will be used under the multivariate normality assumption to impute the missing values by treatment group. To conform to the multivariate normality assumption, baseline and post-baseline TG will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation.

The primary efficacy analysis will take place after the last patient has completed the Week 53/ET visit and the database has been locked. Details of the controlled access to the unblinded data will be outlined in the SAP and Unblinding Plan.

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 baseline and Month 6.
- A nonparametric Wilcoxon rank-sum test will be performed on the percent change in TG from baseline to Month 6. Missing data will be handled using the same multiple imputation method as the primary analysis. The treatment difference will be assessed

using the Hodges-Lehmann estimator of the location shift and corresponding 95% CI. The analysis will be conducted in the FAS.

- A two-dimensional tipping-point analysis will be conducted on the imputed data (based on the primary imputation approach as described above) to assess the influence of missingness on the conclusion of the treatment difference. 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. The analysis will be conducted in the FAS.
- A few sensitivity analyses using controlled imputations (pattern mixture models (PMM)) with ANCOVA similar to that for primary analysis will be conducted in the FAS to assess the robustness of the primary analysis results. With these approaches, missing not at random (MNAR) is assumed and the mean function for the missing data from patients treated with olezarsen who discontinue the study is pre-specified in ways that assess the robustness of the missing at random (MAR) assumption in the primary analysis.
  - Patients with missing TG value at Month 6 will be imputed using a pattern mixture model. Specifically, for patients treated with olezarsen 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 discontinuation 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. The analysis will be conducted in the FAS. Baseline and post-baseline TG will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation.
  - All patients treated with olezarsen 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 using the same multiple imputation method as the primary analysis
  - Patients with missing TG values after treatment discontinuation will have TG values multiply imputed based on the known assessments from the retrieved dropouts (e.g., for Month 6, the retrieved dropouts include those patients who discontinue treatment before Week 25 but still have assessments at Week 25 or 27), if there are a sufficient number of retrieved dropouts. The imputation model will include the following variables: fasting TG values at baseline and post-baseline visits and the multiple imputation will be stratified by treatment group. If there is no sufficient number of retrieved dropouts, missing TG value

after treatment discontinuation at Month 6 or Month 12 will be imputed using a "wash-out" (Jump to Reference, J2R) multiple imputation approach. With the approach, patients treated with olezarsen who discontinue study will have missing post-discontinuation TG values multiply imputed based on baseline fasting TG and history of pancreatitis (yes/no) of the patient, and the imputation model for the placebo group. Patients in the placebo group who discontinue the study will have missing post-treatment discontinuation TG values multiply imputed using the MI method as the primary analysis. Baseline and post-baseline TG will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation.

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 for the primary endpoint.
- The proportion of patients who achieve fasting TG < 150 mg/dL (1.69 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 in the subset of FAS with Baseline TG < 500 mg/dL will be compared between each olezarsen treatment group and pooled placebo group using a logistic regression model with the treatment group as the factor, 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. The analysis will be repeated in the subset of PPS with Baseline TG < 500 mg/dL as a sensitivity analysis. An additional sensitivity analysis will be conducted in the subset of FAS with Baseline TG < 500 mg/dL, in which all patients who have missing data due to discontinuation will be considered as non-responders.
- The proportion of patients who achieve fasting TG < 500 mg/dL at Month 6 and proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 will be analyzed in the same way as the proportion of patients who achieve fasting TG < 150 mg/dL. It will be conducted in the subset of FAS or PPS with baseline TG ≥ 500 mg/dL.
- The percent change in fasting apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1 from Baseline to Months 6 and 12 in the FAS will be analyzed in the same way as for the primary endpoint.
- The adjudicated acute pancreatitis event rates in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment and in the FAS during the Treatment Period (Week 1 through Week 53/ET) will be compared between pooled olezarsen treatment and placebo group using a Negative Binomial regression model or Poisson regression model with the treatment group and log transformed baseline TG 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 Treatment Period will be used as an offset variable. In the case of not enough events to perform the model-based analysis, the number and percentage

of subjects along with the two-sided 95% exact CI using Clopper-Pearson methodology will be summarized based on FAS. Fisher's exact p-value will also be provided.

Additional sensitivity analyses using different imputation models for continuous secondary efficacy endpoints will be conducted. The details will be provided in SAP.

10.6.4 Pharmacokinetic Analysis

Pharmacokinetic (PK) analysis will include the following:

- Determine trough (pre-dose) and post-treatment olezarsen plasma concentrations in all patients who receive Study Drug. For all patients who receive olezarsen treatment, plasma concentrations over time 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 olezarsen treatment, 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 (ADA) analysis will include the following:

- Evaluate immunogenicity (IM) (confirmed positive/negative and, when applicable, titer of anti-olezarsen antibodies) before, during, and after treatment with Study Drug (olezarsen 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- olezarsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or not determinable.
- Determine patient level IM parameters, which will include but may not be 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 proportion of patients who achieve various TG thresholds (e.g., fasting TG < 135 mg/dL, > 2000 mg/dL, etc.) and TG percent reductions (e.g., ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70% reduction, etc.) at Months 6 and 12 will be compared between olezarsen and placebo groups.

The adjudicated MACE incidence rates (number and percent of subjects) and event rates will be summarized by treatment group.

Additional analyses of MACE composite of CV death, non-fatal MI, non-fatal ischemic stroke, and arterial revascularization (coronary and non-coronary), and the triple composite of CV death, non-fatal MI, and non-fatal ischemic stroke may be performed depending on rates of MACE.

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 (olezarsen or placebo) are administered.

Importantly, patients should be informed of the possibility and risks of a reduction in PLT 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 GCP, the Declaration of Helsinki 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 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 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. Also, if new or emerging safety information affect the benefit/risk assessment of the clinical trial negatively, and with review and recommendation by the DSMB, the study would be terminated. 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

Study Week	Screening[A]		Treatment Period																Follow up Period		
	Run-in	Qual[M]	1	5[M]	9[M]	13[M]	17[M]	21[M]	25/ET-L1[M,N]	27/ET-L2[M,N]	29[M]	33[M]	37[M]	41[M]	45[M]	49[M]	51/ET-L3[M,N]	53/ET-L4[M,N] or Tx ET[M]	4[M,O]	8[M,O]	13[M,O] or Post-Tx ET[M]
Study Day	-28 to -15	-14 to -1	1[B]	29	57	85	113	141	169	183	197	225	253	281	309	337	351	365	28	56	91
Visit and Testing Window ± Days	-28	0	-3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Informed Consent	X																				
Medical History	X																				
FSH[C], TSH, free T4	X																				
Hepatitis B, C, HIV	X																				
Inclusion/Exclusion Criteria	X	X																			
Body Weight and Height[D]	X		X						X									X			X
Vital Signs	X		X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Physical Examination	X		X						X									X			X
12-lead ECG	X		X															X			X
Pregnancy Test[E]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Extended Urinalysis[F]	X		X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Chemistry[G,H]	X		X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Hematology[H]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Coagulation (aPTT, PT, INR)	X		X						X									X			
Lipid Panel[G]	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X
HbA1c	X		X						X									X			X
hsCRP	X		X						X									X			X
Anti-drug Antibody (ADA) [I]			X	X		X			X				X					X			X
Plasma PK - olezarsen [I]			X	X		X			X				X					X	X	X	X
Archived Serum & Plasma Samples[H,J]			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
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet/Life-style/Alcohol Counseling[K]	X		X	X		X		X	X		X		X		X			X		X	
Study Drug: SC Injection[L]			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 Screening Period (that may be extended to 8 weeks if assessments can't be completed within the 4-week period) that includes an at least 2-week Diet/life-style Stabilization/Run-In Period and an approximately 2-week Qualification 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] For confirmation of menopause at Screening per inclusion criteria

[D] Height only required at Screening

[E] 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

[F] 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.

[G] Blood samples to be collected after an overnight fast of at least 10 hours. Fasting is not required for confirmatory tests, repeated uninterpretable, or missing tests, or tests taken for safety reasons

[H] If the PLT, renal function, 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 PLT count, liver chemistry, or renal function results will be reviewed promptly (within 2 business days of receipt) by the Investigator. Any case of a PLT count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

[I] PK/ADA samples will be collected prior to dose administration (pre-dose) during Weeks 1-49 of the Treatment Period, and any time at the end of the Treatment Period (Week 53) and during follow up or ET visit, as specified in Appendix C

[J] Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings, cardiometabolic disease relationship, and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of olezarsen. Samples may be stored up to 20 years

[K] Recommended time points for qualified site personnel to reinforce compliance to diet/ life-style modifications and alcohol restrictions (Appendix E)

[L] Study Drug can be administered at home by patient or caregiver after receiving appropriate training

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

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

[O] Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (4 weeks) post-last dose

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 olezarsen 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)
- TSH, free T4

Coagulation
- aPTT
- PT
- INR

Lipid Panel
- Total Cholesterol
- LDL cholesterol (ultracentrifugation)
- HDL cholesterol
- ApoB
- Triglycerides
- VLDL cholesterol
- ApoC-III
- Non-HDL-C
- ApoA-1
- Remnant cholesterol

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]
- Olezarsen (total full length ASO) concentration in plasma

Immunogenicity
- Anti- olezarsen antibodies (ADA)

Other assessments
- HbA1c

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)

Inflammation
- hsCRP

[1]Plasma and immunogenicity samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of olezarsen with plasma constituents.

APPENDIX C. PK AND ADA SAMPLING SCHEDULE

Blood samples for the determination of plasma olezarsen concentrations and ADA assessment will be collected prior to dosing, and at various time points throughout the Post-Treatment Follow-up Period as noted in the table below. Plasma PK and ADA 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 olezarsen with plasma constituents.

Plasma Trough and Post-Treatment Sampling Schedule for all Patients

	Treatment Period						**Follow-up Period**		
Study Week	**1**	**5**	**13**	**25/ET-L1****	**37**	**53/ET-L4** or Tx ET**	**4***	**8***	**13/ Post-Tx ET***
Study Day	**1**	**29**	**85**	**169**	**253**	**365**	**28***	**56***	**91***
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Any time	PK only Any time	PK only Any time	Any time

*Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (4 weeks) post-last dose
**Landmark visit. For early termination (ET-L) visits: Week 25 is ET-L1 and Week 53 is ET-L4

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

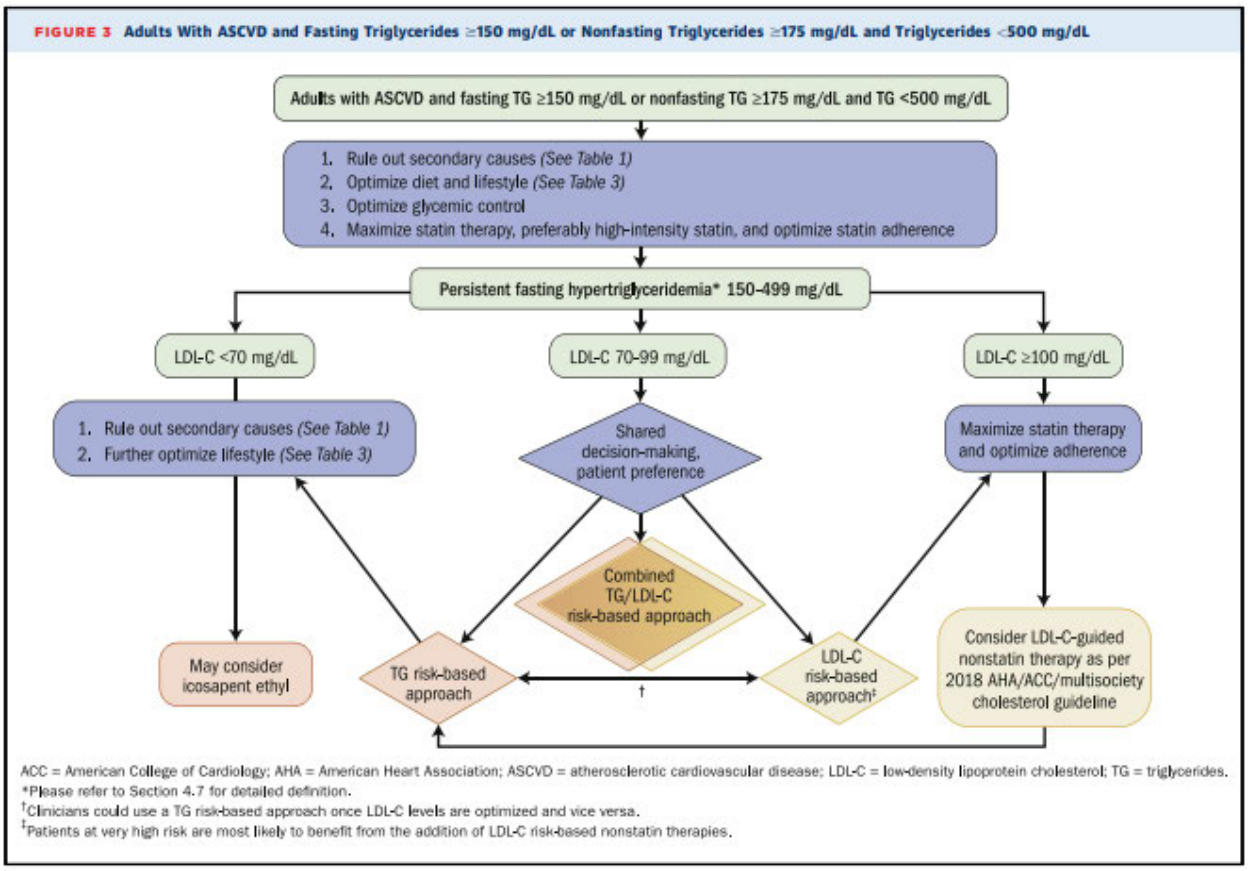
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

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

APPENDIX E. GUIDELINES FOR MANAGEMENT OF HYPERTRIGLYCERIDEMIA (LIFE-STYLE INTERVENTIONS AND STANDARD OF CARE LIPID LOWERING THERAPY)

Management of hypertriglyceridemia should consist of life-style interventions (including optimization of diet, weight loss, intensification of physical activity) and use of lipid-lowering medications as described in the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias (Mach et al. 2020) and the most recent 2021 ACC Expert Consensus Decision Pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia (Virani et al. 2021).

The guidance for the clinical workflow of patients with clinical ASCVD and fasting TGs ≥ 150 mg/dL and < 500 mg/dL (Virani et al. 2021) is shown in the figure below.



The recommended lipid lowering therapies for patients with SHTG are provided below.

1. **If baseline TG levels are 500-879 mg/dL:**
   - Consider fibrate or prescription strength omega-3 fatty acids (icosapent ethyl or omega-3 carboxylic acids)
   - Statin therapy encouraged. If the patient has established ASCVD, diabetes, or is high risk (e.g., > 7.5% 10-yr risk of ASCVD per the Pooled Cohort Equation, or ≥ 5% 10-year risk or fatal CV disease per SCORE), then the patient should be on statin therapy unless intolerant, in which case ezetimibe is strongly suggested
2. **If baseline TG levels are ≥ 880 mg/dL:**
   - Should be on fibrate and/or prescription strength omega-3 fatty acids unless neither is tolerated
   - Should be on statin therapy. Must be on some form of lipid-lowering therapy, ideally statin + TG lowering drug

Dietary Recommendations for patients with hypertriglyceridemia are provided in the table below (Virani et al. 2021).

	TG <500 mg/dL	TG 500-999 mg/dL	TG ≥1,000 mg/dL*	Patient Messages
Alcohol	Restrict Do not exceed limits: 2 drinks/d for men, 1 drink/d for women	Abstain completely	Abstain completely	For patients with TG <500 mg/dL, if alcohol is consumed, wine or beer with lower alcohol content is recommended over beverages with higher alcohol content. Alcohol content is listed on packaging and patients are encouraged to select beverages with lower alcohol content should they chose to consume alcohol.
Sugar-sweetened beverages	Restrict	Abstain completely	Abstain completely	Recommend plain or sparkling water, unsweetened tea, or coffee
Fruits†	Okay to include but individualize—3-4 servings/d	Limit to 3 or 4 servings/d and individualize. Avoid fruits with a high glycemic index (ie, pineapples, mangoes, watermelon, ripe bananas)	Limit to 1 serving/d. Recommend individualized medical nutrition therapy with a registered dietitian nutritionist	Consume whole fruit and avoid fruit juices when possible. Emphasize fresh fruits without added sugar or salt.
Vegetables	Emphasize vegetables	Emphasize vegetables, but avoid vegetables with a high glycemic index (ie, carrots, potatoes, sweet potatoes, yams, parsnips)	Emphasize vegetables, but avoid vegetables with a high glycemic index (ie, carrots, potatoes, sweet potatoes, yams, parsnips)	Avoid canned vegetables with salt and vegetables frozen with sauces. Avoid vegetable juices. Recommend 2.5 cups/d (77)‡
Legumes (beans, lentils, chickpeas, tofu, and so on)	Emphasize	Emphasize	Emphasize	Avoid added salt. Emphasize plant-based proteins instead of red meat. Avoid ultraprocessed meat alternatives.
Fish/seafood	Emphasize fatty fish Recommend at least 2 servings/wk	Emphasize either fatty or lean fish Recommend 2 (or more) servings/wk	Emphasize lean fish Recommend 2 (or more) servings/wk	Examples of fatty fish include salmon, farmed rainbow trout, and tuna. Examples of lean fish or seafood include cod, tilapia, haddock, flounder, and shrimp. Prioritize fresh, frozen, or packaged without sodium.
Poultry/lean meats	Encourage	Encourage	Limit to the very leanest meats	Substitute poultry and lean meats in place of red meat. Avoid processed meats.
Dairy products	Limit full-fat dairy products. Avoid sugar-sweetened dairy products.	Limit full-fat dairy products. Avoid sugar-sweetened dairy products.	Eliminate full-fat dairy products and sugar-sweetened dairy products	Consume fat-free dairy products. Avoid any dairy products with added sugars.
Fiber-rich whole grains	Emphasize 6 servings/d unless a lower-carbohydrate diet is indicated§	Emphasize 4-6 servings/d unless a lower-carbohydrate diet is indicated§	Emphasize individualized medical nutrition therapy with a registered dietician nutritionist	Replace refined grains (white bread, white rice, pasta) with fiber-rich whole-grain cereals, bread, brown rice
Nuts and peanuts	Emphasize	Consume in moderation	Limit	Preferably plain without added sugars or sodium
Total fat **Type of fat**	Moderate fat (30%-35% of calories) ■ Limit SFA and emphasize unsaturated fat	Low fat (20%-25% of calories)‖ ■ Limit SFA and emphasize unsaturated fat	Very-low fat (10%-15% of calories or less) ■ Limit fats to 20-30 g/d or less ■ Meet essential fatty acid requirements ■ For patients who need extra calories, add MCT oil gradually	Emphasize liquid oils (soybean, canola, corn, olive) instead of solid fats, butter, lard, and tropical oils (coconut, palm, and palm kernel)
Cholesterol	Choosing healthy protein foods, dairy products, and fats will limit cholesterol	Choosing healthy protein foods, dairy products, and fats will limit cholesterol	Choosing healthy protein foods, dairy products, and fats will limit cholesterol	
Desserts (sweets, cookies, cakes, pies, other pastries, ice cream, candy)	Occasional indulgence	Occasional indulgence	Abstain completely	
Added sugars (table sugar, jams/jellies, honey)	Occasional indulgence (<6% of calories)	Occasional indulgence (<5% of calories)	Abstain completely/eliminate	

*Nutrition resources for patients are available from the National Lipid Association: https://www.lipid.org/sites/default/files/when_your_tgs_are_over_1000_mgdl.pdf and https://www.learnyourlipids.com/heart-healthy-resources/fcs-cookbook/.
†One serving of fruit = 1 small piece of fruit (apple, orange, pear) or 1/2 cup chopped.
‡Recommendations are based on a 2,000-calorie diet (77).
§Examples include a patient with diabetes or obesity. For these individuals, fewer servings may be indicated.
‖Clinicians may opt to reduce total fat as percent of calories in some of these patients to 10%-15% (examples include those with a history of pancreatitis or those at the higher end of this range).

APPENDIX F. CLINICAL DIAGNOSIS OF ASCVD AND METABOLIC SYNDROME

Clinical Diagnosis of ASCVD:

1. Documented CAD (at least 1 of the following criteria must be satisfied):
   - Angiographic evidence of ≥ 50% stenosis in 1 or more major epicardial coronary arteries
   - Documented prior myocardial infarction
   - History of coronary revascularization (PCI or CABG)
   - Evidence of cardiac ischemia on exercise stress test/imaging
   - Coronary artery calcium (CAC) score > 100
2. Documented cerebrovascular disease (at least 1 of the following criteria must be satisfied):
   - Documented prior ischemic stroke
   - Carotid artery disease with ≥ 50% carotid artery stenosis
   - History of carotid artery revascularization
3. Documented peripheral artery disease (at least 1 of the following criteria must be satisfied):
   - Ankle-brachial index (ABI) < 0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral arterial intervention
   - Amputation involving the lower extremity due to peripheral artery disease

Clinical Diagnosis of Metabolic Syndrome:

Metabolic syndrome is defined by at least 3 of the 5 below (Grundy et al. 2019):

- Elevated waist circumferences, defined as ≥ 102 cm (40.1 inches) (or 90 cm [35.4 inches]) in males and ≥ 88 cm (34.6 inches) (or 80 cm [31.4 inches]) in females*
- Elevated triglycerides ≥ 175 mg/dL (2.0 mmol/L†) or treatment for elevated triglycerides
- Reduced HDL-C < 40 mg/dL (< 1.0 mmol/L) in men, < 50 mg/dl (< 1.3 mmol/L) in women, or drug treatment for low HDL-C
- Hypertension defined a systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension
- Elevated fasting glucose ≥ 100 mg/dL or hemoglobin A1c above the upper limit of normal, or drug treatment of elevated glucose

* Waist circumference cut points generally recommended for the United States are ≥ 102 cm in males and ≥ 88 cm in females, but lower cut points (≥ 90 cm in males and ≥ 80 cm in females) are commonly recommended for other populations.
† Categorical cut point for triglycerides incorporates both fasting and non-fasting triglycerides.

Protocol

Version:	1
Version Date:	24 Mar 2023
Title:	678354-CS8 Protocol - Amend 2: A Randomized, Double-blind, Placebo-Controlled, Ph 2b Study of ISIS 678354 in Patients with Hypertriglyceridemia and Atherosclerotic CD (Established or at Increased Risk for), and/or with Severe

APPROVALS:

PPD PPD , 24-Mar-2023 21:35:36 GMT+0000

1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Version 1.0 (17 October 2023), is provided.

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of Olezarsen (ISIS 678354) in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or with Severe Hypertriglyceridemia
Protocol Number:	ISIS 678354-CS8
Protocol Version/Date:	Protocol Amendment 2/March 22, 2023
Investigational Product:	Olezarsen
Sponsor:	Ionis Pharmaceuticals, Inc.
SAP Version/Date:	Version 1.0/October 17, 2023

CONFIDENTIAL

SIGNATURE PAGE

Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Phase 2b Study of Olezarsen (ISIS 678354) in Patients with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or with Severe Hypertriglyceridemia
Protocol Number:	ISIS 678354-CS8
SAP Version/Date:	Version 1.0/October 17, 2023

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

Signature	**Date**
PPD Ionis Pharmaceuticals, Inc.	
PPD Ionis Pharmaceuticals, Inc.	
PPD Ionis Pharmaceuticals, Inc.	
PPD Ionis Pharmaceuticals, Inc.	

MEDPACE SIGNATURE PAGE

Approved by:

PPD

Digitally signed by PPD
DN: cn=PPD o=Medpace, ou, email=PPD c=US
Date: 2023.10.18 17:44:54 -04'00'

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Date: 2023.10.18 17:35:40 -04'00'

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Medpace

VERSION HISTORY

Version	Version Date	Description
1.0	October 17, 2023	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	Adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
ASCVD	atherosclerotic CV disease
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BUN	blood urea nitrogen
CAD	coronary artery disease
CIR	copy increment from reference
CIs	confidence intervals
CK	creatinine kinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DBP	diastolic blood pressure
DSMB	Data and Safety Monitoring Board
ECGs	electrocardiograms
eCRF	electronic Case Report Form
eDISH	evaluation of Drug Induced Serious Hepatoxicity
ET	early termination
FMQ	FDA Medical Query
FLRs	flu-like reactions
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin a1c
HDL-C	high-density lipoprotein cholesterol
hsCRP	CRP measured by high sensitivity assay
ICEs	intercurrent events
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IM	immunogenicity
ISIS 678354	antisense inhibitor of apoC-III, olezarsen
ISR	Injection site reaction
ITT	intent-to-treat

Abbreviation	Definition
LCRIS	local cutaneous reaction at injection site
LDL-C	low-density lipoprotein cholesterol
LFT	Liver Function Test
LS	least squares
MACE	major adverse cardiovascular event
MACE-AC	MACE-Adjudication Committee
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MNAR	missing not at random
MPV	mean platelet volume
Non-HDL-C	non-high density lipoprotein cholesterol
PAC	Pancreatitis Adjudication Charter
PCI	percutaneous coronary intervention
PK	pharmacokinetic
PMM	pattern mixture models
PPS	per protocol set
PLT	platelet
PT	preferred term
QTcF	QTc interval calculated using Fridericia's formula
Q4W	every 4 weeks
RDW	red cell distribution width
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
SHTG	severe hypertriglyceridemia
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TC	total cholesterol
TG	triglycerides
UACR	urine albumin/creatinine ratio
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VLDL-C	very low-density lipoprotein cholesterol
VR	ventricular rate
WBC	white blood cell
WHO-DDE	World Health Organization - Drug Dictionary Enhanced

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the methodologies, rules, and conventions to be used in the presentation and analysis of the efficacy, safety, and pharmacokinetics (PK) for Protocol ISIS 678354-CS8.

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

- Study Protocol (Amendment 2: Mar 22, 2023)
- electronic Case Report Form (eCRF) (Sep 26, 2023)

Revision(s) of this SAP will not be required for any subsequent amendments to the protocol which do not change the analyses described in this SAP. The SAP will be finalized prior to database lock (DBL). If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after DBL, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be documented in the final clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of olezarsen on percent change in fasting triglyceride (TG) levels compared to placebo.

2.2 Secondary Objectives

To evaluate the effect of olezarsen as compared to placebo on:

- Percent change in fasting TG levels upon longer duration of treatment (1 year)
- Proportion of patients who achieve different thresholds in fasting TG levels
- Percent change in fasting apolipoprotein C-III (apoC-III), very low-density lipoprotein cholesterol (VLDL-C), remnant cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), high- density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apolipoprotein B (apoB), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A-1 (apoA-1)
- Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Adjudicated acute pancreatitis event rate

2.3 Exploratory Objectives

To evaluate the effect of olezarsen on the incidence of major adverse cardiovascular events (MACE)

2.4 Safety and Tolerability Objective

To evaluate safety and tolerability of olezarsen

2.5 PK Objective

To evaluate PK of olezarsen

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

The 678354-CS8 study is a multi-center, randomized, double-blind, placebo-controlled trial done in conjunction with the TIMI Study Group, an academic research organization based at Brigham and Women's Hospital and Harvard Medical School. Eligible patients will enter an approximately 4-week Screening Period (that may be extended to 8 weeks if assessments can't be completed within the 4-week period) that includes an at least 2-week Diet/ life-style Stabilization/Run-in Period, and an approximately 2-week Qualification Period. Following Qualification, approximately 152 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 3:1 to receive olezarsen or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of olezarsen once every 4 weeks (Q4W) or matching volume of placebo (0.5 mL) during Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg olezarsen once Q4W or matching volume of placebo (0.8 mL) during Weeks 1-49 of the Treatment Period. The 80 mg once Q4W may be adjusted to 50 mg once Q4W due to tolerability or safety reasons at any point during the study following consultation with the Sponsor Medical Monitor or designee. Randomization will be stratified by Qualification fasting TG levels of < 500 mg/dL vs ≥ 500 mg/dL. Following the Week 53 visit, patients will enter the 13-week Post-Treatment Follow-up Period. All endpoints will be evaluated after the last patient has completed the Week 53/early termination (ET) Visit.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Percent change in fasting TG from Baseline at Month 6 (average of Weeks 25 and 27) compared to placebo.

3.2.2 Secondary Endpoints

- Percent change in fasting TG from Baseline at Month 12 (average of Week 51 and Week 53) compared to placebo.
- Proportion of patients who achieve fasting TG < 150 mg/dL (1. 69 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline fasting TG < 500 mg/dL (5.65 mmol/L).
- Proportion of patients who achieve fasting TG < 500 mg/dL (5.65 mmol/L) at Month 6 and proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline fasting TG ≥ 500 mg/dL.
- Percent change in fasting apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1 from Baseline at Month 6 and at Month 12 compared to placebo.
- Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment
- Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo

3.2.3 Exploratory Endpoints

- Events rates of independently adjudicated MACE.
- Additional analyses of the broader MACE composite of CV death, non-fatal MI, non-fatal ischemic stroke, or arterial revascularization (coronary or non-coronary)
- The triple composite of CV death, non-fatal MI, and non-fatal ischemic stroke and its individual components (CV death; MI; ischemic stroke) may be performed depending on rates of MACE.

3.2.4 Safety and Tolerability Endpoints

Safety and tolerability assessments include adverse events (AEs), vital signs and weight, physical examinations, clinical laboratory tests, electrocardiogram (ECG), and use of concomitant medications. Safety and tolerability results in patients receiving olezarsen will be compared with those receiving placebo.

3.2.5 PK Endpoints

Plasma trough and post-treatment concentrations of olezarsen, and potential exposure/ response relationship for apoC-III and TG.

4 STATISTICAL METHODOLOGY

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 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 patients, Investigators, study staff, and the Sponsor are to remain blinded to central and local lipid data (TG, apoC-III, TC, HDL-C, remnant cholesterol, apoB, VLDL-C, non-HDL-C, LDL-C, and apoA-1) starting after the first dose on Day 1 then throughout the remainder of the study or as noted for TG or apoB alerts per Section 8.5.7 of the study protocol.

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 serious AEs (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 Acute Pancreatitis Adjudication Charter (PAC). 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 MACE-Adjudication Committee (MACE-AC) as outlined in the MACE Adjudication Charter.

The MACE-AC will adjudicate all fatal events and events suggestive of non-fatal myocardial infarction, hospitalization for unstable angina, hospitalization for (worsening) heart failure, coronary or non-coronary revascularization procedures, or stroke. The criteria used by the MACE-AC to determine the occurrence of any of the events will follow the recommendations included in published Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (Hicks et al. 2018; Thygesen et al. 2018).

4.2 General Considerations

4.2.1 Data Presentation

Descriptive summary statistics including the number of subjects with non-missing data (n), mean, median, standard deviation (SD), standard error of mean (SEM), interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. 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 and SEM 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 n, frequency counts and percentages. Percentages will be rounded to one decimal place unless it is an integer. Percentages will not be presented for zero counts.

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. Where appropriate, p-values will be reported. 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 (CIs) will be presented to one more decimal place than the raw data.

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

Efficacy and safety results will be summarized under the treatment to which patients are randomized. For safety results, should there be any cases after unblinding in which a patient received treatment other than what was randomized, such cases will be discussed and noted in footnotes where applicable.

The efficacy summaries will be presented by the treatment group (placebo, olezarsen 50 mg, olezarsen 80 mg). The disposition, demographics, baseline characteristics, medical history, prior and concomitant medications, and protocol deviations will be presented by treatment group, total olezarsen treated (50 mg + 80 mg) and overall. The safety data will be presented by the treatment group and total olezarsen treated.

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.

Selected safety endpoints will be analyzed using below analysis method:

- The crude incidence rates, risk difference with 95% CI between each active treatment group (or total olezarsen treated) and pooled placebo group. The crude incidence rate (in 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 unstratified Miettinen-Nurminen (MN) method.
- Exposure- adjusted incidence rate (EAIR) rates, EAIR difference with 95% CI between each active treatment group (or total olezarsen treated) and pooled placebo group. EAIR is defined as the number of patients who experienced at least one event times 100 divided by total person-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 in year (i.e., last participation date or data cutoff date minus first dose date plus one day divided by 365.25). The difference of EAIR and 95% CI will be estimated using Wald's method.
- Exposure-adjusted event rate (EAER), defined as the number of events times 100 divided by the total duration in the on-study period in year.

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Medpace (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 listed. Additional listings may be provided for all patients impacted by COVID-19 during conduct of the study. Additional summary (s) and/or analyses may be provided if deemed necessary.

4.2.2 Definition of Baseline, Month 6 and Month 12

Baseline lipid measurements are defined as the average of the pre-dose measurement on Day 1 and all measurements from the Qualification Period. If the Day 1 pre-dose and Qualification Period measurements are all missing, then the last non-missing measurement from the Screening Period will be used as baseline. For lipids other than TG, missing baseline values will be imputed using the multiple imputation method described in Section 4.9.1.4 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.

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.

The Month 6 lipid assessments are defined as the average of non-missing Weeks 25 and 27 fasting assessments. The Month 12 lipid assessments are defined as the average of non-missing Weeks 51 and 53 fasting assessments. For both Month 6 and Month 12, if 1 of the 2 assessments is missing, then the other non-missing assessment will be used.

4.2.3 Analysis Visit Windows

The efficacy measures of fasting lipid panel (TG, APOC-III, VLDL-C, remnant cholesterol, TC, non-HDL-C, apoB, HDL-C, LDL-C, and ApoA-1), including the data from both scheduled and unscheduled visits, will be mapped to analysis visits according to the visit windows in Table 1 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 will be summarized by the visit label provided in the data. No visit windows are needed for the data of post-treatment visits.

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. 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.

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.

Table 1: Analysis Windows (Days)

Efficacy	Nominal Visit (Week)	Target Day	Analysis Visit Window (Day)
Lipid Panel	5	29	2-43
	9	57	44-71
	13	85	72-99
	17	113	100-127
	21	141	128-155
	25	169	156-176
	27	183	177-190
	29	197	191-225
	37	253	226-281
	45	309	282-330
	51	351	331-358
	53	365	359-379[a]

[a]Day 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

Subject disposition will be summarized based on all screened subjects. The summary will include the following information:

- The total number of subjects who were screened, screen failed, randomized, and the major reason of screen failure will be summarized for all screened subjects. The number and percentage of screen failures due to COVID-19 impact will also be summarized.
- The number and percentage of subjects randomized, treated, completed study treatment, early terminated from study treatment, major reasons for early termination of study treatment, completed post-treatment follow-up, early terminated from post-treatment follow-up, major reasons for early termination of post-treatment follow-up, will be presented by treatment group, total olezarsen treated, and overall based on

randomized subjects. The number and percentage of subjects who discontinued treatment or post-treatment follow-up related to COVID-19 will also be summarized.

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

4.4.2 Protocol Deviations

Protocol deviations will be recorded in the eCRF, where they will be classified as "minor" or "major". All protocol deviations and major protocol deviations will be summarized by deviation category, by treatment group, total olezarsen treated, and overall, based on randomized subjects. The number and percentage of subjects with protocol derivation, in each deviation category and due to COVID-19 related impact will be provided for all protocol deviations or major protocol deviations in separate tables. 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 Demographic and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by treatment group, total olezarsen treated, and overall using descriptive statistics based on the FAS, PPS, and Safety Set, separately.

Demographic data include, but are not limited to age, age group (< 65 years, ≥ 65 years), sex, ethnicity, race, height, weight, and body mass index (BMI).

Key baseline laboratory parameters include baseline HbA1c and baseline lipids profile: fasting TG, apoC-III, TC, HDL-C, apoB, remnant cholesterol, VLDL-C, non-HDL-C, LDL-C and apoA-1.

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

4.6 Analysis Sets

For purposes of analysis within this SAP, the following populations are defined:

Full Analysis Set (FAS): All patients who are randomized and received any amount of Study Drug (olezarsen or placebo). The FAS represents the practically feasible intent-to-treat (ITT) population as delineated in International Conference on Harmonization (ICH) Guideline E9. This set 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, have a baseline fasting TG assessment, and who have no significant protocol deviations that could compromise the interpretation of efficacy. Significant protocol deviations will be determined prior to unblinding for statistical analysis. This set will be used for supportive inferences concerning efficacy.

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

PK Set: All patients who are randomized and received any amount of olezarsen and have at least 1 evaluable concentration result post-first dose. This set will be used for analysis of PK data.

The number and percentage of subjects in each analysis set will be summarized by treatment group, total olezarsen treated, and overall based on randomized patients.

A by-subject listing of analysis sets, including the inclusion/exclusion flag for each analysis set and reasons for exclusion from each analysis set, will be provided.

4.7 Medical History

The medical history will be coded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The final MedDRA version used will be designated in the clinical study report. The number and percentage of subjects reporting a medical history will be summarized by SOC, PT and by treatment group, total olezarsen treated, and overall, using the Safety Set.

A by-subject listing of medical history will be provided.

A separate table will be created for the targeted medical history based on the Safety Set. The number and percentage of patients with below targeted medical history terms will be summarized accordingly. A listing of targeted medical history will be provided.

Cardiac-related history:

- Atherosclerotic CV disease [ASCVD]
  - Coronary artery disease [CAD]
    - Angiographic evidence of ≥ 50% Stenosis in 1 or more major epicardial coronary arteries
    - Cardiac Ischemia on exercise stress test/imaging
    - Coronary Artery calcium scan completed with a score >100
    - Myocardial Infarction (MI)
    - Percutaneous coronary intervention [PCI]
    - CABG
  - Cerebrovascular Disease
    - Ischemic Stroke
    - Carotid Artery Disease defined by the ASCVD criterion
      - ≥ 50% carotid artery stenosis
      - Carotid Endarterectomy
      - Carotid artery revascularization(s) other than Carotid Endarterectomy (either surgical or stenting)
  - Peripheral artery disease
    - Peripheral Revascularization
    - Aorto-iliac Revascularization
    - Lower extremity amputations due to Peripheral Artery Disease
    - Ankle-brachial index < 0.9 with symptoms of intermittent claudication
    - Ankle-brachial index < 0.9 without symptoms of intermittent claudication

- TIA
- Any Stroke
- Hemorrhagic Stroke
- Other Cerebrovascular disease
- Unstable Angina
- Heart failure
- Current NYHA Class
- Atrial fibrillation

Other risk factors:

- Diabetes mellitus Type 1
  - Duration (in years) of diabetes mellitus Type 1, duration being calculated as the year of informed consent from (ICF) minus the start year of the disease plus one.
- Diabetes mellitus Type 2
  - Duration (in years) of diabetes mellitus Type 1, duration being calculated as the year of ICF minus the start year of the disease plus one.
- Hypertension requiring pharmacologic treatment
- Smoking
  - Current
  - Former
- Chronic kidney disease
  - stage

Medication history:

- Statins
  - Reason not on statins
- Any other lipid lowering therapy
  - Reason not on lipid lowering therapy

Hematologic disorder history:

- Bleeding diathesis or coagulopathy

Pancreatitis history:

- Acute pancreatitis or any symptoms suggestive of pancreatitis with hospitalization
- Acute pancreatitis or any symptoms suggestive of pancreatitis without hospitalization
- Known Chronic Pancreatitis

Previous Treatment:

- Previous treatment with volanesorsen
- Previous treatment with olezarsen

4.8 Prior and Concomitant Medication

Medication start and stop dates will be compared to the date/time of the first dose of study drug to allow medications to be classified as prior medication, and concomitant medication.

Any medication taken prior to the first dose of study drug will be classified as a prior medication, regardless of whether continued while on treatment or not. Any medication taken on or after the first dose of study drug will be classified as a concomitant medication.

Partial or missing medication start and/or stop date(s) will be imputed by the following imputation rules:

Missing or partial 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

Missing or partial 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 medications will be coded using the World Health Organization - Drug Dictionary Enhanced (WHO-DDE) and summarized by Anatomical Therapeutic Chemical (ATC) drug class, preferred term (PT) and by treatment group, total olezarsen treated and overall based on the Safety Set. Actual versions of WHO-DDE used will be stated in the clinical study report.

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

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

All prior and concomitant medications will be listed based on the Safety Set.

4.9 Efficacy Evaluation

The primary endpoint will be assessed on the FAS and PPS, with the former being the basis for the primary efficacy analysis. All the secondary endpoints will be assessed on the FAS.

4.9.1 Analysis and Data Conventions

4.9.1.1 Hypothesis

The null hypothesis of the primary analysis is that there is no difference between olezarsen and Placebo in the percent change in fasting TG from Baseline at Month 6. The alternative hypothesis is that there is a difference between olezarsen and Placebo in the percent change in fasting TG from Baseline at Month 6.

Symbolically, this is expressed as follows:

H(0) : μ(test) = μ(reference)

H(1) : μ(test) ≠ μ(reference)

4.9.1.2 Multi-center Studies

The term 'Center' will be used to define each investigator site. The study will be conducted at multiple centers in multiple countries. The data from all study centers will be pooled together for the statistical summaries.

4.9.1.3 Adjustments for Covariates

The covariate will include the baseline stratification factor and baseline measurements.

The baseline stratification factor will be classified as two categories below based on the base TG

- Baseline TG ≥ 500 mg/dL (5.65 mmol/L) vs. < 500 mg/dL

4.9.1.4 Handling of Dropouts or Missing Data

Multiple imputation for missing fasting TG at month 6 and/or month 12:

As the randomization stratification factor, the fasting TG at qualification visit will not be missing. Therefore, the baseline fasting TG for all randomized patients will not be missing as the fasting TG at qualification visit will be used to calculate the baseline fasting TG (refer to Section 4.2.2).

Patients with a missing fasting TG at Months 6 and/or 12 will have missing values multiply imputed based on the known assessments from the retrieved dropouts (e.g., for Month 6, the retrieved dropouts include those patients who discontinue treatment before Week 25 but still have assessments at Week 25 or 27; for Month 12, the retrieved dropouts include those patients who discontinue treatment before Week 51 but still have assessments at Week 51 or 53), if there are a sufficient number of retrieved dropouts. The imputation model contains the following variables: baseline fasting TG, fasting TG at each post-baseline visit and the multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999).

If there is no sufficient number of retrieved dropouts, missing TG value after treatment discontinuation at Month 6 or Month 12 will be imputed using a "wash-out" (Jump to Reference, J2R) multiple imputation approach. With the approach, patients treated with olezarsen who discontinue treatment will have missing TG values after the last "observed value" multiply imputed based on baseline fasting TG and the imputation model for the placebo group. Patients in the placebo group who discontinue the treatment will have missing TG values multiply imputed using the baseline fasting TG, fasting TG values at post-baseline visits from the placebo group.

The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing values by treatment group. The variable list for imputations will include the baseline value, as well as all available post-baseline value. To conform to the multivariate normality assumption, baseline and post-baseline fasting TG will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation. The SAS procedure PROC MI will be used to create 1000 imputed datasets. The first 100 imputed datasets with imputed values within the analytical measuring range will be chosen from 1000 imputed datasets for the analysis.

Default 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.

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

Step 1, using PROC MI to generate 1000 imputations:

```
/*************************************************************************     */
/* Note:                                                                        */
/*     baseline = baseline fasting TG                                           */
/*     impute = the iteration number in the multiple imputation                 */
/*     trtpn = Treatment group: 0=Placebo, 1= olezarsen 50 mg, 2 = olezarsen 80 mg*/
/*************************************************************************************/

       proc mi data = TG seed = 2438291 nimpute = 1000 out=TGIM;

              transform log(baseline) log(week5) log(week9) log(week13) log(week17)
              log(week21) log(month6) log(week29) log(week37) log(week45) log(month12);

             mcmc;

             var baseline week5 week9 week13 week17 week21 month6 week29 week37 week45
              month12;
             by trtpn;
       run;
```

Step 2, extract placebo data, fit a GLM model using log transformed data for each imputation and get parameter estimates:

```
proc glm data=pla_mar;
   by paramcd imputation_;
   model AVAL_log=base_log avisitn_interval/solution;
run;
```

Step 3, for patients in the active arm, remove the imputed data post last "observed value", apply the parameter estimates calculated from step 2 to active treatment arms and back transformed the data to create the 1000 imputation datasets.

Step 4: Set the dataset from step 3 and the subset of placebo dataset (the dataset used in step 2) together then choose the first 100 imputation dataset with imputed values within the analytical measuring range.

Multiple imputation for missing fasting lipids (excluding TG) at baseline and Month 6/Month 12:

For other lipid data (apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1), a two-stage multiple imputation approach will be utilized to impute the missing values at baseline, Months 6 and Month12 if baseline is missing for at least one randomized patient for given lipid parameter.

First, the missing baseline fasting lipid value will be multiply imputed based on the observed baseline assessments from other patients. The MCMC method (Schafer 1997; Schafer 1999) will be used to impute the missing values. The imputation model will include baseline fasting lipid value and baseline stratification factor (i.e., baseline fasting TG ≥ 500 mg/dL (yes/no). The baseline lipid value will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation. The SAS procedure PROC MI will be used to create 1000 imputed datasets.

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

```
/*****************************************************************************/
/*  Note:                                                                    */
/*  baseline = baseline fasting lipid value                                  */
/*  stratt = Baseline TG >= 500 mg/dL (5.65 mmol/L) Yes/No                */
/*****************************************************************************/
          proc mi data = adeff seed = 2438291 nimpute = 1000 out= adeff2;
              transform log(baseline);
                   mcmc;
               var stratt 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, the missing lipid value at Months 6 and/or 12 will be imputed using similar method described above for missing fasting TG at month 6 and/or month 12, with an imputation model that contains the following variables: baseline fasting lipid value, fasting lipid value at each post-baseline visits and baseline stratification factor. The multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999).

The following pseudo SAS code and seed (2438291) will be used for the second stage of imputation:

```
/*****************************************************************************/
/*  Note:                                                                    */
/*  baseline = baseline lipid parameter                                      */
/*  trtpn = treatment group: 0=placebo, 1=olezarsen 50 mg, 2=olezarsen 80 mg  */
/*  _imputation_ = the iteration number in the stage 1 imputation            */
/* stratt = baseline TG >= 500 mg/dL (5.65 mmol/L) Yes/No                */
/*****************************************************************************/
proc sort data=adeff2;
   by _imputation_;
run;
proc mi data=adeff2 (where=(trtpn=0)) seed=2438291 nimpute=1 out=imputed;
/*repeat the procedure for each treatment group by replacing trtpn category in the
where option*/
   transform log(baseline) log(week5) log(week9) log(week13) log(week17) log(week21)
log(month6) log(week29) log(week37) log(week45)  log(month12);
   mcmc;
   var baseline stratt week5 week9 week13 week17 week21 month6 week29 week37 week45
month12;
   by _imputation_;
run;
```

For lipid parameters with no missing data at baseline, the baseline imputation will not be performed. The second stage of imputation will be performed to create 1000 imputed datasets. The following pseudo SAS code and seed (2438291) will be used for multiple imputation:

```
/*****************************************************************************/
/*  Note:                                                                    *
/*  baseline = baseline lipid parameter                                      */
/*  trtpn = treatment group: 0=placebo, 1=olezarsen 50 mg, 2=olezarsen 80 mg  */
/*  stratt = baseline TG >= 500 mg/dL (5.65 mmol/L) Yes/No                */
/*****************************************************************************/

proc mi data=adeff seed=2438291 nimpute=1000 out=adeff2;
   transform log(baseline) log(week5) log(week9) log(week13) log(week17) log(week21)
log(month6) log(week29) log(week37) log(week45) log(month12);
   mcmc;
   var stratt baseline week5 week9 week13 week17 week21 month6 week29 week37 week45
month12;
by trtpn;
run;
```

The Step 2, 3 and 4 similar to that for TG imputation with an additional factor of baseline TG stratification factor will be used to create 100 imputation datasets.

4.9.1.5 Multiple Comparisons/Multiplicity

The multiplicity will be controlled by using a hierarchical ranking strategy in the following testing sequence. All tests will be conducted at a two-sided alpha level of 0.05. For the primary endpoint family, the 2 treatment arms will be compared against placebo using the hierarchical testing procedure, in which the olezarsen 80 mg treatment group will be compared to the placebo at the 2-sided alpha level of 0.05, if the comparison is statistically significant ($p < 0.05$), then the olezarsen 50 mg treatment group is compared against the placebo at the alpha level of 0.05. If the comparison of the olezarsen 80 mg treatment group to placebo group is not statistically significant, then the comparison of the olezarsen 50 mg treatment group against placebo and all

secondary endpoints will be considered exploratory. The order of the testing on the secondary endpoints is outlined below. The endpoint ranked as first will be tested and the difference will be declared statistically significant if the p value is less than 0.05. In case that the difference for the first endpoint is statistically significant, the endpoint ranked as second will be tested, and the difference will be declared statistically significant if the p-value is less than 0.05. The testing will continue as long as the previously ranked endpoint is statistically significant. If the secondary endpoints are not evaluated as a part of the hierarchical testing procedure due to previously ranked endpoint was not statistically significant, the statistical tests will be reported and interpreted in a descriptive manner.

1. Primary endpoints family:
    - Primary endpoint: Comparison of percent changes in fasting TG from Baseline to Month 6 between olezarsen 80 mg treatment group and placebo in the FAS
    - Primary endpoint (not co-primary endpoint): Comparison of percent changes in fasting TG from Baseline to Month 6 between olezarsen 50 mg treatment group and placebo in the FAS
2. Secondary endpoints will be tested in the FAS according to the following sequence:
    - Comparison of percent change in fasting TG from Baseline to Month 12 between olezarsen 80 mg and placebo group
    - Comparison of percent change in fasting TG from Baseline to Month 12 between olezarsen 50 mg and placebo group
    - Comparison of percent change in fasting apoC-III from Baseline to Month 6 between olezarsen 80 mg and placebo group
    - Comparison of percent change in fasting apoC-III from Baseline to Month 12 between olezarsen 80 mg and placebo group
    - Comparison of percent change in fasting apoC-III from Baseline to Month 6 between olezarsen 50 mg and placebo group
    - Comparison of percent change in fasting apoC-III from Baseline to Month 12 between olezarsen 50 mg and placebo group
    - Comparison of proportion of patients who achieve fasting TG < 150 mg/dL at Month 6 between olezarsen 80 mg and placebo group in the subgroup of FAS with baseline fasting TG < 500 mg/dL
    - Comparison of proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 between olezarsen 80 mg and placebo group in the subgroup of FAS with baseline fasting TG < 500 mg/dL
    - Comparison of percent change in fasting VLDL-C from Baseline to Month 6 between olezarsen 80 mg and placebo group
    - Comparison of percent change in fasting VLDL-C from Baseline to Month 12 between olezarsen 80 mg and placebo group
    - Comparison of percent change in fasting VLDL-C from Baseline to Month 6 between olezarsen 50 mg and placebo group
    - Comparison of percent change in fasting VLDL-C from Baseline to Month 12 between olezarsen 50 mg and placebo group
    - Comparison of percent change in fasting non-HDL-C from Baseline to Month 6 between olezarsen 80 mg and placebo group

- Comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting non-HDL-C from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of proportion of patients who achieve fasting TG < 150 mg/dL at Month 6 between olezarsen 50 mg and placebo group in the subgroup of FAS with baseline fasting TG < 500 mg/dL
- Comparison of proportion of patients who achieve fasting TG < 150 mg/dL at Month 12 between olezarsen 50 mg and placebo group in the subgroup of FAS with baseline fasting TG < 500 mg/dL
- Comparison of percent change in fasting HDL-C from Baseline to Month 6 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting HDL-C from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting HDL-C from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting HDL-C from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting remnant cholesterol from Baseline to Month 6 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting remnant cholesterol from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting remnant cholesterol from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting remnant cholesterol from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting apoB from Baseline to Month 6 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting apoB from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting apoB from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting apoB from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting ApoA-1 from Baseline to Month 6 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting ApoA-1 from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting ApoA-1 from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting ApoA-1 from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting LDL-C from Baseline to Month 6 between olezarsen 80 mg and placebo group

- Comparison of percent change in fasting LDL-C from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting LDL-C from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting LDL-C from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting total cholesterol from Baseline to Month 6 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting total cholesterol from Baseline to Month 12 between olezarsen 80 mg and placebo group
- Comparison of percent change in fasting total cholesterol from Baseline to Month 6 between olezarsen 50 mg and placebo group
- Comparison of percent change in fasting total cholesterol from Baseline to Month 12 between olezarsen 50 mg and placebo group
- Comparison of proportion of patients who achieve fasting TG < 500 mg/dL at Month 6 between olezarsen 80 mg and placebo in the subgroup of FAS with baseline fasting TG ≥ 500 mg/dL
- Comparison of proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 between olezarsen 80 mg and placebo in the subgroup of FAS with baseline fasting TG ≥ 500 mg/dL
- Comparison of proportion of patients who achieve fasting TG < 500 mg/dL at Month 6 between olezarsen 50 mg and placebo in the subgroup of FAS with baseline fasting TG ≥ 500 mg/dL
- Comparison of proportion of patients who achieve fasting TG < 500 mg/dL at Month 12 between olezarsen 50 mg and placebo in the subgroup of FAS with baseline fasting TG ≥ 500 mg/dL
- Comparison of adjudicated acute pancreatitis event rate during the Treatment Period between pooled olezarsen treatment group and placebo
- Comparison of adjudicated acute pancreatitis event rate during the Treatment Period between pooled olezarsen treatment group and placebo in the subset of FAS with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment in FAS

4.9.1.6 Interim Analyses

There is no interim analysis planned for the study.

4.9.1.7 Examination of Subgroups

Subgroup analyses of the primary efficacy and applicable secondary endpoints will be made to assess consistency of analysis results over subgroups. The subgroups include but are not limited to:

- Baseline fasting TG ≥ 500 mg/dL vs. < 500 mg/dL
- Baseline fasting TG ≥ 200 mg/dL vs. < 200 mg/dL
- age groups (< 65, ≥ 65 years)
- race (White vs non-White)
- Sex (male, female)
- ethnicity (Hispanic or Latino vs. Not Hispanic or Latino)

- Baseline BMI (< 25, 25 to < 30, 30 to < 40, ≥ 40 kg/m^2)
- diabetic status (diabetic vs non-diabetic)
- Baseline Hemoglobin A1C (HbA1c): < 6.5 vs. ≥ 6.5
- Baseline background therapies (lipid-modifying therapy versus none; statins versus no statins; Fibrates vs. no Fibrates)
- Previous treatment with volanesorsen: Yes vs. No

4.9.2 Primary Efficacy Variable

The primary efficacy variable is the percent change from Baseline to Month 6 (average of Weeks 25 and 27) in fasting TG.

4.9.2.1 Primary Analysis

The primary efficacy analysis will take place after the last patient has completed the Week 53/ET visit and the database has been locked.

The primary analysis of the primary endpoint is to compare the percent change from Baseline to Month 6 in fasting TG between each olezarsen treatment group vs. placebo group using the FAS.

If patients have intercurrent event(s) before Week 25, 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 a missing TG value at Month 6 will have TG imputed, details are described in Section 4.9.1.4.

The attributes and description of the estimands are provided in the tables below:

Treatments	• olezarsen 80 mg • placebo
Participant Population	Patients with hypertriglyceridemia and atherosclerotic cardiovascular disease (ASCVD) (established, or at increased risk for), or with severe hypertriglyceridemia (SHTG) as defined by protocol eligibility criteria
Variable	Percent change from Baseline to Month 6 (average of Weeks 25 and 27) in fasting TG
Intercurrent events (ICEs) and strategies	• Discontinuation of study treatment prior to Week 25 *Treatment policy strategy* • Disallowed concomitant therapy/procedure prior to Week 25 *Treatment policy strategy*
Population-level summary	Difference in means of percent change between olezarsen 80 mg and placebo in the FAS
Description of estimand	The difference in means of percent change from Baseline to the Month 6 in fasting TG between olezarsen 80 mg and placebo (regardless of early treatment discontinuation, use of additional medication, or change in background or concomitant treatments) in patients with hypertriglyceridemia and ASCVD (established, or at increased risk for), or with SHTG

For each of the 100 imputed datasets obtained from Section 4.9.1.4, the percent change from Baseline to Month 6 in fasting TG will be compared between olezarsen treatment groups and placebo using an analysis of covariance (ANCOVA) model that assumes unequal variance with precent change from Baseline to Month 6 in fasting TG as the dependent variable, treatment group (olezarsen 80 mg, olezarsen 50 mg, or Placebo) as factor, and natural log-transformed baseline fasting TG as a covariate.

The pseudo SAS code of ANCOVA:

```
/*************************************************************************      */
/* Note:                                                                        */
/*     baseline = baseline TG                                                   */
/*     impute = the iteration number in the multiple imputation                 */
/*     trtpn = Treatment group: 0=Placebo, 1= olezarsen 50 mg, 2 = olezarsen 80 mg*/
/*     pchg = percent change TG from baseline to Month 6                        */
/*************************************************************************      */

          data TG; set TG;
             logbase = log(baseline);   /* log transformed baseline*/
          proc mixed data = TG;
             by impute;
             class trtpn;
      model pchg = trtpn logbase/ ddfm=satterth;
             lsmeans trtpn/e diff cl;
             estimate 'olezarsen 50 mg vs Placebo' trtpn -1 1 0;
             estimate 'olezarsen 80 mg vs Placebo' trtpn -1 0 1;
          run;
```

The model will provide an estimate of Least Squares (LS) Mean of percent change from baseline in fasting TG for each treatment group as well as the treatment differences relative to the placebo group and the corresponding standard error.

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

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

4.9.2.2 Sensitivity Analysis of Primary Endpoint

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

Sensitivity Analysis 1:

The primary analysis with ANCOVA model for percent change in fasting TG from Baseline to Month 6 will be repeated in the PPS.

Sensitivity Analysis 2 - Completer Set:

The primary efficacy analysis with ANCOVA model for percent change in fasting TG from Baseline to Month 6 will be repeated in a subset of patients in the FAS with no missing TG value at baseline and Month 6.

Sensitivity Analysis 3:

A nonparametric Wilcoxon rank-sum test will be performed on the percent change in TG from baseline to Month 6 based on FAS. Missing data will be handled using the same multiple imputation method as the primary analysis. The estimates from the fitted model 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 olezarsen 80 mg group and placebo group. The same approach will be used for comparison between olezarsen 50 mg group and placebo group.

The example SAS code can be found below:

```
/*************************************************************************/
/* Note:                                                                 */
/*  pchg = percent change of TG from baseline to Month 6                 */
/*  impute = the iteration number in the multiple mutation               */
/*  trtpn = treatment group: 0=placebo, 1=olezarsen 80 mg                */
/*************************************************************************/
proc npar1way data= TGIM hl alpha=0.05;
   class trtpn;
   var pchg;
   by impute;
run;
```

Sensitivity Analysis 4 - Tipping point analysis using 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 4.9.1.4 in the SAP:

1. For the placebo group, a positive constant shift ($\delta_{c,}$, %) will be added to or subtracted from the percent change of imputed TG values at the primary time point. The shift will gradually increase.
2. For each value of the placebo shift parameter, a positive constant shift (δ_t, %) will be added to or subtracted from the percent change of 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 4.9.1.4 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 δc and δt will be determined post-hoc in order to define reasonable increments.

Sensitivity Analysis 5 - Exploring the robustness of the primary analysis (FAS):

A few sensitivity analyses using controlled imputations (pattern mixture models (PMM)) with ANCOVA will be conducted in the FAS to assess the impact of alternative missing data assumptions on the robustness of the primary analysis results.

- Patients treated with olezarsen who discontinue the treatment due to AE (i.e., informative missing), their missing TG data after the last "observed value will be multiply imputed using the copy increment from reference (CIR) approach (Carpenter et al. 2013)[7] based on the estimates from of the placebo patients. The assumption is when a patient discontinues treatment due to informative missing, they continue to take advantage of their previous therapy, but from discontinuation onwards he/she would progress in the same way as the patients in the placebo group (i.e., parallel to the profile for 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. The reason for this is that it is assumed those patients would have proceeded in the future, in a comparable way to similar patients (with similar baseline and covariates) in their own treatment who did remain in the trial. The analysis will be conducted in the FAS. Baseline and post-baseline fasting TG will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation.
- All patients treated with olezarsen who discontinue the treatment will have missing TG values after the last "observed value multiply using the CIR approach based on the estimates from the placebo patients. Missing TG for placebo patients will be imputed using the MI method as the primary analysis.

Baseline and post-baseline fasting TG will be natural log-transformed before the imputation process, the data will be back transformed to create the imputed data set after the imputation.

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

The percent change from Baseline to Month 6 in fasting TG between each olezarsen treatment group (olezarsen 80 mg, olezarsen 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 Month 6, x is the baseline value of fasting TG; treatment group as factor 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 SEM. 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 Month 6 will have fasting TG value multiply imputed using the multiple imputation methods described in Section 4.9.1.4 in the SAP.

4.9.3 Secondary Efficacy Variables

To control the type I error, a hierarchical ranking strategy will be employed with the sequence of endpoints defined as in Section 4.9.1.5.

4.9.3.1 Percent Change in Fasting TG From Baseline at Month 12

The percent change in fasting TG from Baseline to Month 12 (average of Week 51 and Week 53) in the FAS will be analyzed in the same way as for the primary endpoint.

The same set of sensitivity analyses (sensitivity analysis 1 to sensitivity analysis 6) and subgroup analysis as for the primary endpoint will be conducted for the percent change in fasting TG from Baseline to Month 12.

4.9.3.2 Proportion of Patients Who Achieve Fasting TG < 150 mg/dL at Month 6 and at Month 12 in the Subgroup of Patients with Baseline fasting TG < 500 mg/dL

The proportion of patients who achieve fasting TG < 150 mg/dL (1.69 mmol/L) at Month 6 and Month 12 in the subset of FAS with Baseline fasting TG < 500 mg/dL (5.65 mmol/L) will be compared between each olezarsen treatment group and placebo group using a logistic regression model with the treatment group as the factor, and natural 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. For each of the 100 imputed datasets obtained from Section 4.9.1.4, the logistic regression model described above will be fitted and the estimates from each of 100 fitted model will be combined to provide an overall odds ratio with corresponding CIs and p-value.

Sensitivity Analysis 1:

An additional sensitivity analysis will be conducted in the subgroup of FAS with Baseline fasting TG < 500 mg/dL, in which all patients who have missing data due to discontinuation will be considered as non-responders.

Sensitivity Analysis 2:

A 2-dimensional tipping-point analysis will be conducted in the subgroup of FAS with Baseline fasting TG < 500 mg/dL using the imputed data based on the primary imputation approach as described in Section 4.9.1.4 in the SAP. Similar to the sensitivity analysis 5 for the primary endpoint, a positive constant shift values (%) will be added to or subtracted from the percent change of the imputed TG values at each time point of interest until the tipping points are reached.

4.9.3.3 Percent Change in Fasting ApoC-III, VLDL-C, Remnant Cholesterol, Non-HDL-C, HDL-C, TC, ApoB, LDL-C, and ApoA-1 From Baseline at Month 6 and at Month 12

The percent change in fasting apoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, apoB, LDL-C, and apoA-1 from Baseline to Months 6 and Month 12 in the FAS will be analyzed in the way similar to that for the primary endpoint using an ANCOVA model with precent change from Baseline to Month 6 or Month 12 in fasting value as the dependent variable, treatment group (olezarsen 80 mg, olezarsen 50 mg, or Placebo) and baseline stratification factor as factors, and natural log-transformed baseline value as a covariate.

The sensitivity analyses using the imputation models as described in sensitivity analysis 3 and 5 for the primary endpoint will be conducted.

4.9.3.4 Proportion of Patients Who Achieve Fasting TG < 500 mg/dL at Month 6 and at Month 12 in the Subgroup of Patients with Baseline fasting TG ≥ 500 mg/dL

The proportion of patients who achieve fasting TG < 500 mg/dL at Month 6 and Month 12 will be analyzed in the same way as the proportion of patients who achieve fasting TG < 150 mg/dL. It will be conducted in the subset of FAS with baseline fasting TG ≥ 500 mg/dL. Tipping point analysis will not be performed.

4.9.3.5 Adjudicated Acute Pancreatitis Event Rate During the Treatment Period in the FAS

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 PAC. 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. 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 adjudicated acute pancreatitis event rates will be compared between pooled olezarsen treatment and placebo group using a Negative Binomial regression model or Poisson regression model with the treatment group and natural log transformed baseline fasting TG 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 Treatment Period will be used as an offset variable.

From the models, the mean rate and SEM for each treatment group as well as the mean rate ratio relative to the placebo group and corresponding 95% CIs 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 the 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 Negative Binomial regression model can be found below:

```
/*****************************************************************************/
/* Note*/
/*  logbase     = log transformed baseline TG                                */
/*  trtpn = treatment group: 0=pooled placebo, 1=olezarsen 80 mg or 50 mg    */
/*  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);
run;

proc genmod data=pan;
   class trtpn;
   model numevent = trtpn  logbase  num5year/dist=negbin link=log
      offset = logtime;
   /* update "dist=negbin" to "dist=poisson" for Poisson regression model*/
   lsmeans trtpn/diff cl exp ilink;
run;
```

In the case of not enough acute pancreatitis events to perform the model-based analysis, the number and percentage of subjects with the acute pancreatitis event along with the two-sided 95% exact CI using Clopper- Pearson methodology will be summarized based on FAS. Fisher's exact p-value will also be provided.

4.9.3.6 Adjudicated Acute Pancreatitis Event Rate during the Treatment Period 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.

4.10 Safety Evaluation

All safety summaries will be based upon the Safety Set. By-visit safety data will be presented using visit label as recorded on the eCRF per Schedule of Procedures in Appendix A of the protocol.

4.10.1 Extent of Exposure and Treatment Compliance

The duration of exposure to olezarsen will be calculated as follows:

- Treatment exposure (days) = date of last Study Drug administration – date of first administration + 28
- Treatment exposure (months) = Treatment exposure (days)/30
- Treatment Compliance (%) = (actual total dose injected [mg]) / (expected total dose to be administered during the treatment period [mg]) × 100.

Note that for patients who early terminated from treatment, denominator should be based on the total doses expected (mg) until discontinuation.

The following summaries will be provided by treatment group and olezarsen treated and listed based on Safety Set:

- A summary of the treatment exposure in both days and months, total number of doses administered, and the total amount of study drug received (mg)
- A summary of treatment compliance (%).

- Number of patients with dose interruption, dose interruption due to AE, and number of patients with study drug reduced.
- Descriptive 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

4.10.2.1 Definition of Treatment-Emergent Adverse Event (TEAE)

TEAEs are defined as adverse events that occurred on or after the first administration of Study Drug or worsened relative to the pre-treatment state. Note that imputed dates will be used for defining TEAEs.

In addition, if 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” AEs will be defined based on AE start date, and AE start date of the second record will be the same as AE stop date of the first record. AE severity (mild/moderate/severe) should be compared pairwise between these linked events when defining TEAEs. Consider 2 cases below:

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

If the AE severity 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 will be deemed as a TEAE.

All TEAEs identified based on the rules above will be summarized in the event number analysis.

4.10.2.2 Analysis for TEAEs

All AEs will be coded to SOC and PT using the MedDRA. The final MedDRA version used will be designated in the clinical study report. The frequency and incidence of AEs will be summarized by SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in descending frequency order within each SOC. Subjects reporting more than one AEs will be counted only once for each level of summation (most severe incident for the severity tables and most related incidence for the relationship tables).

The frequency of patients with any incidences of AEs and the number of events will be presented by treatment group and total olezarsen treated for the following summaries:

- Any TEAEs by SOC and PT
- Any TEAEs by PT
- TEAEs related to Study Drug by SOC and PT. Related is defined as “Related”, “Possible”, or missing relationship to Study Drug

- Any TEAEs by maximum severity, SOC and PT. At each severity level of subject summarization, a subject is classified according to the highest reported severity if the subject reported one or more events. TEAEs with missing severity will be categorized as "Missing" for this summary.
- TEAEs related to Study Drug by severity, SOC, and PT
- Serious TEAEs by SOC and PT
- Serious TEAEs related to Study Drug by SOC and PT
- Serious TEAEs related to Study Drug by SOC and PT
- Serious TEAEs by severity
- Serious TEAEs related to study drug by severity
- TEAEs leading to permanent Study Drug discontinuation by SOC and PT
- TEAEs related to Study Drug leading to permanent Study Drug discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAE with an incidence rate > 5% in any treatment group by PT
- Non-serious TEAE with an incidence rate > 5% in any treatment group by PT

An overall summary of frequency and incidence of AEs of above unique categories will be provided by treatment group and total olezarsen treated. By-subject listing of all AEs will be provided, in which non-treatment emergent AEs will be included and be noted. The following additional listings will be provided for TEAEs unless otherwise specified.

- Listing of treatment-emergent SAEs
- Listing of TEAEs related to study drug
- Listing of TEAEs leading to discontinuation of Study Drug
- Listing of all deaths

To define TEAEs, the algorithm in Section 4.10.2.3 will be applied to impute missing or partial start date or end date. Original reported dates will be used for listings.

4.10.2.3 Missing Date for Adverse Events

For AEs, the following imputation rules will be applied to impute missing dates under conservative principles. The imputed dates will be used for defining TEAEs.

For start dates:

- 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.

For end dates:

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.

4.10.2.4 Adverse Events of Special Interest

The following AEs are considered AE of special interest for the study. These events will be reviewed and evaluated to determine if they meet the criteria.

- Platelet count < 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 irrespective of a MB or CRNMB event.
- Use of medications (prophylactic treatment 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.

Those events will be individually reviewed and evaluated to determine if they meet the criteria.

The following analyses will be provided.

- The number and percentage of patients experiencing events as well as the total number of reported events, risk difference and its 95% CI in the crude incidence rates between each active treatment group (or total olezarsen treated) and pooled placebo group, classified by PT, will be tabulated by treatment group and total olezarsen treated.
- A cumulative incidence plot if data supported.
- EAIR, risk difference and its 95% CI in EAIRs between each active treatment group (or total olezarsen treated) and pooled placebo group, and EAER. classified by PT, will be tabulated by treatment group and total olezarsen treated.

4.10.2.5 Other Adverse Events of Interest

The number and percentage of patients experiencing events as well as the number of reported events, risk difference and its 95% CI in the crude incidence rates between each active treatment group (or total olezarsen treated) and pooled placebo group, classified by PT (unless otherwise specified), will be tabulated by treatment group for the following AEs of Interest.

4.10.2.5.1 Bleeding TEAEs

Bleeding TEAEs will be analyzed by SOC and PT for the following categories.

- 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

4.10.2.5.2 Thrombocytopenia TEAE

Thrombocytopenia TEAE will be analyzed as follows:

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

4.10.2.5.3 Hypersensitivity TEAE

Hypersensitivity TEAEs will be analyzed for the following categories.

- 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 search, incorporates broad and narrow FMQ preferred terms to maximize sensitivity) by PT.
- Serious TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuation in Hypersensitivity FMQ (broad search, incorporates broad and narrow FMQ preferred terms to maximize sensitivity) by PT
- Action taken with drug due to TEAEs in the Hypersensitivity FMQ (broad search, incorporates broad and narrow FMQ preferred terms to maximize sensitivity)
- Rescue medication used in management TEAEs in Hypersensitivity FMQ (broad search, incorporates broad and narrow FMQ preferred terms to maximize sensitivity)
- 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 including selected laboratory tests will be provided.

4.10.2.5.4 Renal Impairment TEAE

Renal impairment TEAEs will be analyzed for the following categories.

- Renal impairment TEAEs (defined based on the 'Acute renal failure' SMQ (narrow and broad)) by SOC and PT
- 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
- Patients who met the original criteria and revised criteria in the renal monitoring and stopping criteria and patients who discontinued study treatment or post treatment follow-up due to TEAEs in Acute Kidney Injury (AKI) FMQ (narrow or broad)
- For patients having 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 having 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 graphical patient profile including but not limited to eGFR (by CKD-EPI formula 2021), serum creatinine, UACR, UPCR and selected electrolytes will be provided.
- For patients who had serious AKI TEAE (FMQ narrow or broad), or discontinued study drug due to AKI TEAE (FMQ narrow or broad) or protocol defined renal monitoring or stopping criteria (original or revised), a data listing including eGFR (by CKD-EPI formula 2021), serum creatinine, UACR and UPCR will be provided.

4.10.2.5.5 Abnormal Liver Function TEAE

Abnormal liver function TEAEs will be analyzed for the following categories.

- Abnormal liver function TEAE (defined based on the 'Drug related hepatic disorders – comprehensive search' SMQ (narrow and broad)) by SOC and PT
- TEAEs, Serious TEAEs, drug-related TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuation in Hepatic Injury and Hepatic Failure FMQ (narrow) by PT
- TEAEs in Hepatic Injury and Hepatic Failure FMQ (narrow) by PT
- Patients who discontinued study treatment or post treatment follow-up due to AEs in Hepatic Injury or Heptic Failure FDA Medical Query (FMQ) (narrow), Lab abnormality (last on treatment ALT ≥ 2 x ULN, AST ≥ 2 x ULN, ALP ≥ 2 x ULN, total bilirubin ≥ 1.5 x ULN) for patients in above categories will also be tabulated.

The number and percentage of patients experiencing events as well as the total number of reported events, classified by PT (unless otherwise specified), will be tabulated by treatment group for the following AEs of Interest.

4.10.2.5.6 Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe AEs 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 2 days (i.e., event onset date on the day of injection and resolution date not on the day of injection or the day after 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 by PT for each treatment group and total olezarsen treated. 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 LCRIS will be summarized by moderate, severe severity and discontinuation of Study Drug due to AE at injection site.

Percentage of injections leading to LCRIS will be calculated as follows for each subject: (A/B)*100, where A = number of injections with an 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 and the time to onset of the first event will be summarized descriptively by treatment group and total olezarsen 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, the number of injections prior to the first LCRIS will also be summarized descriptively by treatment group and total olezarsen treated.

The LCRIS events will be provided in a listing.

4.10.2.5.7 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 2 days or ongoing. ISR will be summarized by PT for each treatment group and total olezarsen treated.

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 and the time to onset of the first event will be summarized descriptively by treatment group and total olezarsen 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, the number of injections prior to the first ISR will also be summarized descriptively by treatment group and olezarsen treated.

ISR will be listed by preferred term.

4.10.2.5.8 Flu-like Reactions

Flu-like reactions (FLRs) will also be summarized by PT for each treatment group and total olezarsen treated.

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

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

Percentage of injections leading to flu-like reactions will be calculated as follows for each subject: (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.

FLRs will be listed by preferred term.

4.10.3 Clinical Laboratory Evaluation

4.10.3.1 General Analysis of Safety Laboratory Data

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

- **Clinical Chemistry:** Sodium, Potassium, Chloride, Bicarbonate, Total Protein, Albumin, Calcium, Magnesium, Phosphorus, Glucose, Blood Urea Nitrogen (BUN), Creatinine, Uric Acid, Total bilirubin, Direct (conjugated) bilirubin, Indirect (unconjugated) bilirubin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Creatinine kinase (CK), and Gamma-glutamyl transferase (GGT)
- **Hematology:** Red blood cells, Hemoglobin, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red cell distribution width (RDW), Platelets (PLTs), Mean platelet volume (MPV), White blood cells (WBCs), and WBC differential (percentage and absolute) (Neutrophils, Eosinophils, Basophils, Lymphocytes, and Monocytes)
- **Coagulation:** activated partial thromboplastin time (aPTT), prothrombin time, international normalized ratio (INR)
- **Other assessments:** Hemoglobin A1C (HbA1c)

- **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). The screening test data will only be displayed in patient listings.
- **Urinalysis:** Color, Appearance, Specific gravity, pH, Protein, Blood, Glucose, Ketones, Bilirubin, Urobilinogen, Leukocyte esterase, Nitrate, Microscopic examination, Urinary protein/creatinine (UPCR) ratio, Urine albumin/creatinine ratio (UACR). The expanded urinalysis data will be only displayed in patient listings. Urine albumin/creatinine ratio (a/c ratio) and protein/creatinine ratio (p/c ratio) will be summarized.
- **Inflammation:** CRP measured by high sensitivity assay (hsCRP)

If the quantitative data were reported as "< X", i.e., below the lower limit of quantification, or "> X", i.e., above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries/figures, but will be presented as recorded (i.e., "< X" or "> X") in the listings.

The following clinical laboratory summaries will be provided by treatment group and total olezarsen treated.

- Quantitative assessments will be summarized using descriptive statistics in terms of observed values, change and percent change from Baseline for each laboratory parameter by scheduled study visit.
- Qualitative assessments will be summarized by frequency counts and percentages by scheduled study visit.

By-subject listings of all laboratory data will be provided based on randomized patients.

4.10.3.2 Additional Analyses of Key Safety Abnormal Laboratory Data

The following categories of key safety laboratory data will be evaluated over the whole post-baseline period. The number and percent of patients with post-baseline results falling in each category below will be tabulated by treatment group and total olezarsen treated. Percentage is calculated using the number of subjects with at least one post-baseline result meet the specific criteria listed below as numerator and the number of subjects with at least one non-missing post-baseline value as denominator. The risk differences and corresponding 95% CIs between each active treatment group (total olezarsen treated) and pooled placebo group will be provided for the selected categories. Results with visit labels as "Unscheduled" will be included in the abnormality summary.

Liver enzyme elevation

- ALT or AST≥ ULN
- ALT or AST≥ 3 × ULN and ALT or AST ≥ 2 × baseline
- ALT/AST ≥ 3 × ULN, ≥ 5 × ULN, ≥ 8 × ULN, ≥ 10 × ULN, or ≥ 20 x ULN, for patients having elevation in liver enzymes (ALT ≥ 3 × ULN), the time to onset of the first event will be summarized using descriptive statistics
- Total bilirubin ≥ 2 x ULN, ≥ 5 x ULN, ≥ 8 x ULN
- Direct bilirubin ≥ 2 x ULN, ≥ 5 x ULN

- Highest post-baseline value of ALT/AST fall in: ≥ 3 × ULN - < 5 × ULN, ALT ≥ 5 × ULN - < 10 × ULN, ALT ≥ 10 × ULN - < 20 × ULN (the risk difference will not be provided for this category)
- ALT or AST ≥ 3 x ULN and Total bilirubin ≥ 2 x ULN
- GGT ≥ 2 × ULN
- ALP ≥ 2 × ULN
- ALP ≥ 3× ULN
- ALP ≥ 2 x ULN and (Baseline ALP < 2 x ULN or Baseline ALP missing)
- ALT or AST ≥ 3 x ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was ≥ ULN) and Total bilirubin ≥ 2 x ULN and ALP ≥ 2 x ULN
- ALT/AST ≥ 3 x ULN and INR ≥ 1.5
- 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 post-baseline results will be tabulated by treatment group and total olezarsen treated. 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.

- ALT or AST ≥ 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed
- ALT/AST ≥ 3 × ULN, ≥ 5 × ULN, ≥ 10 × ULN, or ≥ 20 x ULN, which is confirmed
- 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
- 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 and ALP ≥ 2 × ULN
- 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** INR ≥ 1.5

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 and at least 2-fold increases from Baseline, a listing of all of the ALT, AST, total bilirubin, direct bilirubin, GGT, INR, and ALP records for those patients will be provided. The confirmed values (i.e., at least 3-fold or greater elevations above the ULN for ALT or AST (or the greater of 2 × baseline value or 3 × ULN if the baseline value was ≥ ULN) will be flagged.

Individual spaghetti plots of the ALT, AST, total bilirubin, direct bilirubin, INR, GGT, and ALP for those patients having single value at least 3-fold or greater elevations above the ULN for ALT or AST or for patients with baseline ALT or AST ≥ ULN and at least 2-fold increases from Baseline will be provided in separate files.

Additionally, evaluation of Drug Induced Serious Hepatoxicity (eDISH) dot plot where the X-axis is the ratio of peak ALT and ULN and the Y-axis is the ratio of peak total bilirubin and ULN will be provided by treatment group and total olezarsen treated. The eDISH plot for AST versus total bilirubin will also be provided.

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 and total olezarsen treated:

- Serum creatinine ≥ 0.3 mg/dL higher than baseline
- Serum creatinine ≥ 1.5 × baseline, ≥ 2.0 × baseline, and ≥ 3.0 × baseline
- eGFR (by CKD-EPI formula 2021) decrease from Baseline ≥ 25%, 30%, 50%, 75%, for patients having eGFR ≥ 25% decrease from baseline, the time to onset of the first event will be summarized using descriptive statistics
- UPCR ≥ 500, 1000, 2000 mg/g
- UACR ≥ 300, 500, 600, 1200 mg/g

A listing of the creatinine, eGFR (by CKD-EPI formula 2021), UPCR, UACR values over time will be provided for each patient with single value meeting any of criteria below.

Individual spaghetti plots of the Serum Creatinine, UPCR, UACR, eGFR (by CKD-EPI formula 2021) for patients with single value meet any of criteria below will be provided in separate files.

- eGFR (by CKD-EPI formula 2021) decrease from Baseline ≥ 25%
- UPCR ≥ 500 mg/g Serum creatinine ≥ 1.5 × baseline
- Serum creatinine ≥ 0.3 mg/dL higher than baseline

Shift table for eGFR (by CKD-EPI formula 2021), UPCR and LDL-C will be provided. The categories for the shift table will be:

- eGFR (by CKD-EPI formula 2021): < 30, ≥ 30 and < 60, ≥ 60 mL/min/1.73 m^2
- UPCR: < 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 mg/dL to < 190 mg/dL and ≥ 190 mg/dL

The numbers and percentages of subjects 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).

- Any single occurrence of platelet count < 140,000/mm^3
- Any confirmed platelet count < 140,000/mm^3
- Any single occurrence of platelet count < 100,000/mm^3, 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
- Any confirmed platelet count < 100,000/mm^3
- Any single occurrence of platelet count < 75,000/mm^3
- Any confirmed platelet count < 75,000/mm^3
- Any single occurrence of platelet count < 50,000/mm^3
- Any confirmed platelet count < 50,000/mm^3
- Any single occurrence of platelet count < 25,000/mm^3

- Any confirmed platelet count < 25,000/mm^3
- Worst post-baseline value falling in: 100,000 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)
- Confirmed worst post-baseline value falling in: 100,000 to < 140,000/mm^3, 75,000 to < 100,000/mm^3, 50,000 to < 75,000/mm^3, 25,000 to < 50,000/mm^3, 0 to < 25,000/mm^3
- Worst post-baseline platelet reduction from Baseline ≥ 30% and ≥ 50%
- Confirmed worst platelet reduction from Baseline ≥ 30% and ≥ 50%
- Any 2 occurrences of platelet count < 140,000/mm^3 on different days
- Any 2 occurrences of platelet count < 140,000/mm^3 on different days or any single occurrence of platelet count < 100,000/mm^3

Individual spaghetti plots of the Hemoglobin, hematocrit (HCT), WBC, Platelets, aPTT, PT will be provided for patients with single or confirmed platelet values < 100,000/mm^3 or platelet reduction from Baseline ≥ 30% or have any Adverse Event of Special Interest or have any bleeding events.

Graphs of Mean (±SEM) for key safety lab parameters (i.e., ALT, AST, Total bilirubin, ALP, Hemoglobin, hematocrit (HCT), WBC, Platelets, aPTT, INR, PT, Serum Creatinine, UACR, UPCR, eGFR (by CKD-EPI formula 2021), HbA1c), change and percent change from Baseline at each scheduled visit will be generated.

The correlation between anti-platelet antibodies and platelet decreases as well as immunogenicity (IM) status may be explored if supported by data.

The following hematology and hepatic enzymes lab results will be categorized based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017 with modifications specified in APPENDIX D of the protocol and the incidence of shift from Baseline to worst post-baseline value taken after the first dose will be summarized. Appendix A provides the grading scale summary for these selected analytes based on the guidance above. Of note, grade 0 was added to present non-missing lab values that do not meet the criteria for any Toxicity Grading Scale. 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”.

- Hemoglobin: shift from Baseline to minimum post-baseline value
- WBCs: shift from Baseline to minimum post-baseline value
- Platelets: shift from Baseline to minimum post-baseline value
- Creatinine: shift from Baseline to maximum post-baseline value
- Total Bilirubin: 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
- Platelets: shift from Baseline to confirmed minimum post-baseline value
- ALT: shift from Baseline to confirmed maximum post-baseline value
- AST: shift from Baseline to confirmed maximum post-baseline value

Individual data listings of laboratory results will be presented for each subject. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings.

Hypersensitivity Related Analyte Abnormalities

The number and percentage of patients falling in each abnormality category outlined below will be calculated based on the worst post-baseline assessments.

- Eosinophils > 650 cells/µL, > 1500 cells/µL, > 5000 cells/µL
- WBC > 10,800 cells/µL, > 13,000 cells/µL, > 15,000 cells/µL

4.10.4 Vital Signs and Physical Findings

4.10.4.1 Vital Signs

Vital signs data will include pulse rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), body temperature (°C), weight (kg), height (cm), and body mass index (BMI) (kg/m^2).

Descriptive statistics of observed values, change and percent change from baseline will be presented for each vital sign parameter by scheduled study visit.

Number and percentage of subjects falling in each of the following categories will be tabulated by treatment group and total olezarsen treated:

- Maximum change from baseline in SBP > 5, > 10, > 15, > 20, > 30 mmHg
- Maximum change from baseline in DBP > 5, > 10, > 15, > 20, > 30 mmHg
- Maximum change from baseline in pulse rate > 5, > 10, > 15, > 20 beats/min

A by-subject listing of vital signs data (include change from baseline for weight and BMI), including unscheduled visit, will be provided.

4.10.4.2 Physical Examinations

At Screening, any physical examination findings will be recorded on Medical History. At any other visit, any worsening or new condition findings will be recorded as an AE. Thus, physical examination will be assessed through medical history and AE summaries. A by-subject listing of physical examinations will be provided.

4.10.5 12-Lead Electrocardiograms (ECGs)

ECGs will be performed at the visits indicated in the protocol Schedule of Procedures. The ECG data will include ventricular rate (VR), 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 results, the change and percent change from baseline to each scheduled study visit, will be presented in summary tables; The categorical responses to overall interpretation at each visit will be summarized by counts and percentages.

The following summary tables will be provided by treatment group and total olezarsen treated:

- A summary of each ECG parameter by visit
- A summary of the number and percentage of subjects with QTcF interval exceeding the following predefined upper limits: > 450 msec, > 480 msec, > 500 msec.
- Shift table from baseline to the worst (highest) post-baseline QTcF interval. The categories for the shift table will be: ≤ 450 msec, > 450 msec to ≤ 480 msec, > 480 msec to ≤ 500 msec, and > 500 msec.
- A summary of the number and percentage of subjects experiencing an increase from baseline in QTcF interval of greater than 30 msec or 60 msec at any time post-baseline. This analysis will be presented for all subjects in the Safety Set and for the subgroup whose QTcF is normal at baseline. Normal QTcF is defined as ≤ 450 msec for males or ≤ 470 msec for females. Subjects will be counted only once if they had more than one such event, so only a subject's worst post-baseline value will be considered.

All the ECG data will be listed.

4.10.6 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 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

PK analysis will include the following, using PK Population:

- Plasma concentrations of olezarsen (measured as total full-length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated olezarsen), 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 cohort, treatment, actual dose, gender, patient ID, patient immunogenicity (IM) status, and study day. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "BLQ". Percent differences between nominal and actual dose, as well as between scheduled and actual sampling times will also be listed for all patients. For all patients who receive olezarsen treatment, olezarsen plasma trough (pre-dose) and post-treatment concentrations will be summarized using descriptive statistics by cohort, treatment, dose, study day, and scheduled time point, with and without stratification by subject level ADA data (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 (percentage difference between scheduled and actual sampling time greater than 30%),

or large deviations between actual dose and nominal dose (percent difference between planned 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 olezarsen treatment, 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 subject level ADA data.
- 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 (IM) 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-olezarsen 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 unknown, and when applicable, titer of anti-olezarsen antibodies) before, during, and after treatment with study drug (olezarsen 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 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 Patient Level ADA Data

Patient overall ADA status (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, patient overall ADA status will be assigned 'Unknown'.

Furthermore, patients 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 biologic 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 patient 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.
- Patient 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 patient has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed negative; "Unknown" if the patient 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 (treatment-induced or treatment-boosted ADA) was observed, will be calculated 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 collected - 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 patient

- 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 patient
- Total number of ADA Samples evaluated (NOADASAMT): the total number of ADA samples being collected and analyzed successfully with reportable results for the patient

Lastly, patients with positive ADA status may further be classified as being transient or persistent ADA response, if there are sufficient number of patients 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 patient 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. Patient level IM parameters (as described above), if applicable, will be listed for by treatment and dose for all evaluable patients, 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 Selected PK, PD, Efficacy, and Safety Measures

- The impact of IM on selected PK, PD, efficacy, and safety measures will be evaluated by stratifying plasma PK exposure measures (such as plasma trough and post-treatment olezarsen concentrations, etc.), selected PD, clinical efficacy endpoints and safety measures by patient level ADA data, summarized using typical descriptive statistics, and presented graphically and/or in tables. Efficacy measures to be stratified by patient level ADA data will include but may not be limited to apoC-III and TG levels. Safety measures to be stratified by patient level ADA data will include but may not be limited to AEs, and lab tests for hematology, liver and kidney functions, as appropriate.

Lastly, other stratifications (e.g., based on antibody titer, onset of ADA, patient 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 Analyses

4.11.3.1 The Adjudicated MACE Incidence Rates

The adjudicated MACE incidence rates (number and percent of subjects), exposure adjusted incidence (EAIR) and event rates (EAER) will be summarized by treatment group and total olezarsen treated. Additional analyses of MACE composite of CV death, non-fatal MI, non-fatal ischemic stroke, or arterial revascularization (coronary or non-coronary), and the triple composite of CV death, non-fatal MI, or non-fatal ischemic stroke may be performed depending on rates of MACE. The event rate will be calculated as number of adjudicated treatment emergent MACEs divided by the total duration of follow-up time.

4.11.3.2 Summary of Lipid Parameters

All lipid data including results, absolute changes and percent changes from Baseline will be summarized using descriptive statistics by treatment group, total olezarsen treated and study visit. The means plus/minus SEMs for results, absolute changes and percent changes will be plotted over time by treatment group.

4.11.3.3 Response Rates

The response rates based on various TG threshold (fasting TG < 135 mg/dL; < 150 mg/dL; > 2000 mg/dL in subgroup of patients with baseline fasting TG ≤ 2000 mg/dL) and TG percent reductions (≥ 40%, ≥ 50%, ≥ 60%, ≥ 70% reduction) at Month 6 and Month 12 will be compared between each olezarsen treatment group and pooled placebo group using a logistic regression model with the treatment group and natural 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.

4.12 Determination of Sample Size

With 33 patients in each olezarsen treatment group and 22 in the placebo group, there would be an approximately 80% power to detect a 60% difference between each olezarsen treatment group and placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the olezarsen treatment patients, no change in the placebo patients, and a common SD of approximately 73%.

Approximately 152 patients will be enrolled in this trial to account for potential early dropouts.

4.13 Changes to Protocol-planned Analyses

In protocol, it states: 'All primary and secondary endpoints will be assessed on the FAS and PPS, with the former being the basis for the primary efficacy analysis.' The secondary endpoints on PPS will not be assessed in this SAP.

In protocol, it states: The missing TG value at Months 6 or 12 will be imputed using an imputation model that contains the following variables: baseline fasting TG, fasting TG at each post-baseline visits and the multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999). The missing value imputation method for the primary analysis is updated in the SAP as below:

The retrieved dropouts multiple imputation approach will be used for imputing missing values after discontinuation for the primary efficacy analysis. If there is not a sufficient number of retrieved dropouts, a placebo washout multiple imputation approach will be used for imputing missing values for the primary efficacy analysis.

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6 APPENDICES

6.1 Appendix A – Grading Scale for Selected Lab Analytes with Abnormal Values

Parameter	Unit	Mild	Moderate	Severe
Hemoglobin Decreased (Anemia)	g/dL	< LLN - 10.0	< 10.0–8.0	< 8.0
WBC Decreased	cell/mm^3	< LLN - 3,000	< 3,000–2,000	< 2,000
Platelets Decreased	cell/mm^3	< LLN - 75,000	< 75,000–50,000	< 50,000
Creatinine Increased		> ULN-1.5 × ULN if baseline normal > 1.0–1.5 × baseline if baseline abnormal	> 1.5–3.0 × ULN if baseline normal > 1.5–3.0 × baseline if baseline abnormal	> 3.0 × ULN if baseline normal > 3.0 × baseline if baseline abnormal
ALT, AST Increased		> ULN-3.0 × ULN if baseline normal > 1.5–3.0 × baseline if baseline abnormal	> 3.0–5.0 × ULN if baseline normal > 3.0–5.0 × baseline if baseline abnormal	> 5.0 × ULN if baseline normal > 5.0 × baseline if baseline abnormal
Total Bilirubin Increased		> ULN-1.5 × ULN if baseline normal > 1.0–1.5 × baseline if baseline abnormal	> 1.5–3.0 × ULN if baseline normal > 1.5–3.0 × baseline if baseline abnormal	> 3.0 × ULN if baseline normal > 3.0 × baseline if baseline abnormal

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