

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218614Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	218614
Priority or standard	PRIORITY
Submit date(s)	4/19/2024
Received date(s)	4/19/2024
PDUFA goal date	12/19/2024
Division/office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Review completion date	12/17/2024
Established/proper name	olezarsen sodium
(Proposed) proprietary name	Tryngolza
Pharmacologic class	APOC-III-directed antisense oligonucleotide
Other product name(s)	olezarsen sodium
Applicant	IONIS PHARMACEUTICALS INC
Dosage form(s)/formulation(s)	Injection: 80 mg/0.8 mL in a single-dose autoinjector.
Dosing regimen	80 mg administered by subcutaneous injection once monthly
Applicant-proposed indication(s)/ population(s)	As an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)
SNOMED CT code for proposed indication disease term(s)¹	1197489003 familial chylomicronemia syndrome
Regulatory action	Approval
Approved dosage (if applicable)	80 mg administered by subcutaneous injection once monthly
Approved indication(s)/ population(s) (if applicable)	As an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)
SNOMED CT code for approved indication disease term(s)¹	1197489003 familial chylomicronemia syndrome

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADA	antidrug antibody
AE	adverse event
AI	autoinjector
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	acute pancreatitis
ApoB	apolipoprotein B
ApoC-III	apolipoprotein C-III
AR	adverse reaction
ASCVD	atherosclerotic cardiovascular disease
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BE	bioequivalence
BP	blood pressure
BSA	body surface area
BSEP	bile salt export pump
BSV	between subject variability
CFB	change from baseline
CIR	copy increment from reference
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CRO	Contract Research Organization
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
CVD	cardiovascular disease
CWRES	conditional weighted residuals
CYP	cytochrome P450
DAE	adverse event leading to treatment discontinuation
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
EC ₅₀	half maximal effective concentration
ECG	electrocardiogram
ECL	electrochemiluminescence
eCTD	electronic common technical document
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
E_{max}	maximum effect
EOP2	end-of-phase 2
ER	emergency room
FAS	full analysis set

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FCS	familial chylomicronemia syndrome
FDA	Food and Drug Administration
FLR	flu-like reaction
FMQ	FDA Medical Dictionary for Regulatory Activities Query
GalNAc	N-acetyl galactosamine
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	good laboratory practice
GOF	goodness-of-fit
HD	high dose
HDL-C	high-density lipoprotein cholesterol
HI	hepatic impairment
HR	heart rate
hsCRP	high-sensitivity C-reactive protein
HTG	hypertriglyceridemia
HV	healthy volunteer
IC ₅₀	half maximal inhibitory concentration
IND	investigational new drug
INR	international normalized ratio
ISR	injection site reaction
k _a	absorption rate constant
K _{out}	first-order elimination rate
LCRIS	local cutaneous reaction at the injection site
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantitation
LPL	lipoprotein lipase
LS	least squares
MACE	major adverse cardiac event
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MFH	malignant fibrous histiocytomas
mITT	modified intent-to-treat
MRHD	maximum recommended human dose
MSD	MesoScale Discovery
NCI-CTCAE	National Cancer Institute–Common Terminology Criteria for Adverse Event
NDA	new drug application
NOAEL	no observed adverse effect level
OB	Office of Biostatistics
OLE	open-label extension
OTC	over-the-counter
pcVPC	vision-corrected visual predict check
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PPS	per-protocol set
PRO	patient-reported outcome

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PT	prothrombin time
Q/F	apparent intercompartmental clearance
Q1M	every 30 days
Q4W	every 4 weeks
RR	reference range
RSE	relative standard error
RUV	residual unexplained variability
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SEE	substantial evidence of effectiveness
SMQ	Standardised Medical Query
SOC	system organ class
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
TK	toxicokinetic
T _{max}	time to maximum concentration
UACR	urine albumin/creatinine ratio
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
Vc/F	apparent central volume
VLDL-C	very low-density lipoprotein cholesterol
Vp/F	apparent peripheral volume
WBC	white blood cell

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Ionis Pharmaceuticals (Applicant) submitted this new drug application (NDA) for olezarsen sodium (tradename Tryngolza), seeking approval of this APOC-III-directed antisense oligonucleotide to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS), a rare genetic disorder. Patients with FCS have very high concentrations of triglycerides (TG) and are at increased risk for acute pancreatitis, a potentially fatal complication of this disease. The NDA was reviewed by a multidisciplinary review team. Each discipline recommends approval for adult patients with FCS for the reduction of triglycerides and the signatory authority for this application concurs with those recommendations.

Substantial evidence of effectiveness for olezarsen in patients with FCS was established using data from one adequate and well-controlled trial with confirmatory evidence (CE). A single trial in patients 18 years of age and older with FCS showed a large and clinically significant reduction in triglycerides that was statistically significant compared to placebo along with a numerical decrease in pancreatitis events; all patients were on a background of low-fat diet and optimized triglyceride-lowering therapy. Confirmatory evidence providing strong mechanistic support includes the well-established etiology of the disease, the mechanism of action of the therapy, and trial results in a related condition in patients with moderate to severe hypertriglyceridemia.

The available safety data show that olezarsen is safe for its intended use. Common adverse reactions included injection site reactions, decreased platelet count, and arthralgia. Laboratory test abnormalities included decreases in platelet count and increases in glucose, liver enzymes, and low-density lipoprotein cholesterol (LDL-C). These laboratory changes were notable but did not lead to clinical adverse events. Elevations in liver enzymes were more frequent in patients with moderate hypertriglyceridemia as compared to those patients with FCS. All the identified safety risks for olezarsen can be adequately mitigated through labeling and further evaluated during routine and enhanced pharmacovigilance.

The NDA includes appropriate preapproval nonclinical studies, and no additional nonclinical studies or clinical pharmacology studies will be conducted as postmarketing requirements. We are requesting a postmarketing requirement to complete the ongoing trials in patients with severe hypertriglyceridemia to evaluate further the potential for drug induced liver injury with olezarsen. Enhanced pharmacovigilance will be requested for cases of liver toxicity.

As described in the Benefit/Risk Framework below, we conclude that the reduction in triglycerides, a surrogate for the reduction in risk for acute pancreatitis, observed with use of olezarsen outweighs the risks when olezarsen is used as recommended in the approved labeling.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Familial chylomicronemia syndrome (FCS) is a rare genetic disorder. Individuals have very high concentrations of triglycerides (TG) and are at increased risk for acute pancreatitis, a potentially life-threatening consequence of this condition. Reduction of serum TG levels in patients with severe hypertriglyceridemia (TG $\geq$ 500 mg/dL) is considered a surrogate for reduction of the risk of acute pancreatitis. Olezarsen is a new molecular entity and would be first-in-class for the treatment of FCS, for which there are no FDA-approved therapies.

Primary evidence of olezarsen's efficacy on TG reduction in adult patients with FCS was demonstrated by a single trial, ISIS 678354-CS3. In this 53-week, double-blind, placebo-controlled, randomized trial of adult subjects with FCS, olezarsen 80 mg as an add-on to background TG-lowering therapy decreased TG at Month 6 (average of Weeks 23, 25, and 27) by 44.5% (95% confidence interval [CI]: -72, -17; $p=0.0015$ compared to placebo)¹. The treatment effect with olezarsen was seen in adult subjects with fasting TG levels $\geq$ 880 mg/dL despite low-fat diet ($\leq$ 20 grams fat per day) and optimized lipid lowering therapies and was similar across important subgroups. Over the 12-month treatment period, the numerical incidence of pancreatitis in subjects treated with olezarsen 80 mg was lower compared with placebo (one subject reported 1 event of adjudicated acute pancreatitis (AP) in the olezarsen 80 mg group compared with 11 events experienced by seven subjects in the placebo group). The results of this trial are not typical for the clinical trajectory of FCS and support the efficacy of olezarsen in this population.

The approval decision for olezarsen also relies on confirmatory evidence from a related indication from Trial ISIS 678354-CS8. Trial CS8 demonstrated efficacy on TG lowering for this same dose, 80 mg administered Q4W as a subcutaneous (SC) injection for 1 year, in adults with hypertriglyceridemia (HTG) and atherosclerotic cardiovascular disease (established or at increased risk for), and/or with severe HTG (sHTG). The results from Trial CS8 are similar to those observed in Trial CS3. In Trial CS8, the difference between the olezarsen 80 mg group and the placebo group in percent change in fasting TG from baseline to Month 6 (average of Weeks 25 and 27) was -56.5% (95% CI: -67.4%, -45.6%; $p<0.0001$)². No subjects in any treatment group had an adjudicated AP event during the treatment period in this trial. At Month 6, placebo-adjusted mean percent change in fasting non-high-density lipoprotein cholesterol (non-HDL-C) levels from baseline for olezarsen 80 mg was -24.5% (95% CI: -37.6, -11.5) and for apolipoprotein B (ApoB) was -19.3% (95% CI: -29.8, -8.8)³. This randomized, controlled trial

¹ See Table 11: Primary Analysis: Mean Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 6 (Full Analysis Set), Trial C3 in Section 6.2.2.6.

² See FDA results from Table 31: Primary Analysis Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 6 (Full Analysis Set) in Section 6.2.3.6.

³ See Table 33: Secondary Endpoint: Percent Change in Baseline in Fasting Non-high-density-lipoprotein Cholesterol (mg/dL) at Months 6 and 12 (Full Analysis Set) and Table 35: Secondary Endpoint: Percent Change in Baseline in Fasting Total Apolipoprotein B (mg/dL) at Months 6 and 12 (Full Analysis Set)–Section 6.2.3.6.

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was highly persuasive, having demonstrated a large treatment effect on TG, a highly statistically significant result, and reassuring changes on secondary lipid endpoints.

Typically, two adequate and well-controlled trials are required to achieve the statutory definition of substantial evidence. However, in the case of FCS, given the rarity of the condition, the seriousness of the disease, the unmet medical need to treat this disease, the persuasiveness of the results of Trial ISIS 678354-CS3, and the robustness of the confirmatory evidence in subjects with moderate or severe HTG, the Division of Diabetes Lipid Disorders and Obesity concludes that the Applicant has provided the SEE required by law [see 21 CFR 314.126(a)(b)] to support approval.

Although this application relies primarily on a single, blinded, placebo-controlled trial, the results constitute SEE in this serious, rare condition with a well-characterized natural history. The application supports approval of olezarsen, administered SC 80 mg monthly, as an adjunct to low-fat diet for the treatment of adults with FCS.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive condition leading to a deficiency in lipoprotein lipase (LPL) enzyme activity from inactivation of the LPL gene or genes encoding its co-factors (such as apolipoprotein CII). • Prevalence of FCS is 1 to 10 in 1,000,000 individuals. • Characterized by severely elevated chylomicrons and plasma triglycerides. • The most serious complication is acute pancreatitis, which can be life-threatening. • Other clinical manifestations include eruptive cutaneous xanthomas, lipemia retinalis, episodic abdominal pain, and hepatosplenomegaly.	• FCS is a rare genetic disorder of lipid metabolism characterized by excessive chylomicronemia and severe hypertriglyceridemia. • The most serious complication is acute pancreatitis. Other severe and debilitating symptoms include abdominal pain, fatigue, and depression.
Current treatment options	• Restrictive low-fat diet (<20 grams daily) is the mainstay of therapy that can lower triglycerides, but adherence is difficult. • Other triglyceride-lowering agents, such fibrates, niacin, or omega-3 fatty acids, are generally not effective in FCS. • No approved drug therapies	• Current management of the disease is severe dietary restriction. There is no effective drug therapy, and there exists a high unmet need for effective and safe treatment.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of olezarsen in patients with FCS was evaluated in a single phase 3 trial (CS3). • Randomized (1:1 ratio to Cohort A [50 mg] or Cohort B [80 mg]; each cohort was further randomized 2:1 to groups receiving either the olezarsen dose for the cohort or a matching volume of placebo, respectively), double blind, placebo control, 53-week trial of 66 subjects with FCS, enriched for history of acute pancreatitis or symptoms suggestive of pancreatitis (80%), evaluating olezarsen 50 or 80 mg administered subcutaneously once every 4 weeks versus placebo. – Primary endpoint of mean percent change in fasting TG levels from baseline to Month 6 for olezarsen 80 mg compared with placebo: 33% decrease in TG versus 11% increase for pooled placebo; placebo-adjusted mean percent decrease of 44.5% (p=0.0015; 95% CI: -72.0, -17.0). – Treatment difference persisted over time: placebo adjusted percent change in TG levels from baseline was -61.4% (95% CI: -101.9, -20.8) at Month 12 in the olezarsen 80 mg treated group. – At Month 6, placebo-adjusted mean percent decreases in fasting non-HDL-C levels from baseline for olezarsen 80 mg was 25.7% (95% CI: -44.3, -7.1) – During the Treatment Period, 1 subject had 1 event of adjudicated acute pancreatitis in each of the olezarsen treatment groups (total n = 2) compared with 11 events by 7 subjects in the placebo group. – Approximately 88% or 38/43 subjects in the pooled olezarsen treatment group completed the one-year trial. Three (14%) subjects in the olezarsen 80 mg group compared to 1 (4%) subject in the placebo group discontinued study drug.	• Olezarsen has demonstrated benefit to patients with FCS characterized by lower TG levels which are expected to reduce the risk of pancreatitis. • Olezarsen 80 mg was tolerated by the majority of subjects. • The triglyceride results were compelling, the reduction in acute pancreatitis events was reassuring, and the discontinuation rate was acceptable.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Confirmatory mechanistic evidence from Study CS8, randomized (3:1 allocation within 50 mg and 80 mg Cohorts), double-blind, placebo-controlled, 53-week trial of olezarsen 80 mg or olezarsen 50 mg once every 4 weeks in 154 subjects with hypertriglyceridemia (HTG) and established or increased risk of atherosclerotic cardiovascular disease (ASCVD), or with severe HTG (sHTG). Approximately 90% had baseline TG levels < 500 mg/dL. – Primary endpoint of mean percent change in fasting TG levels from baseline to Month 6 compared with placebo: 64% decrease in TG with olezarsen 80mg versus 8% for placebo; placebo-adjusted mean percent decrease of 56.5% (p<0.0001; 95% CI: -67.4, -45.6).^a – Treatment difference persisted over time: Placebo adjusted percent change in TG levels from baseline was -54.1% (95% CI: -65.8, -42.52)^b at Month 12 in the olezarsen 80 mg treated group. – At Month 6, placebo-adjusted mean percent decrease in fasting non-HDL-C levels from baseline for olezarsen 80 mg was 24.5% (95% CI: -37.6, -11.5) and for apoB was 19.3% (95% CI: -29.8, -8.8).^c – No subjects in any treatment group had an adjudicated acute pancreatitis event during the Treatment Period. – Approximately 82% or 94/115 subjects in the pooled olezarsen treatment group completed the one-year trial. Seven subjects (12%) in the olezarsen 80 mg group and 3 subjects (8%) in the placebo group discontinued study drug.	

Risk and risk management	• In CS3, 43 subjects with FCS were exposed to olezarsen. Twenty-two subjects were treated with olezarsen 80 mg every 4 weeks with a median exposure of 52 weeks (mean, 46 weeks). • In CS8, 57 subjects were treated with olezarsen 80 mg every 4 weeks with a median exposure of 52 weeks (mean, 48 weeks). • Supportive data include CS13, an open-label extension of CS3 in 54 subjects with FCS treated with olezarsen 80 mg every 4 weeks with a median exposure of 33 weeks (mean, 35 weeks). • Supportive data include CS7, an open-label study in 24 subjects with FCS previously treated with volanesorsen, switched to olezarsen 80 mg every 4 weeks. The median duration of exposure was 52 weeks (mean 47 weeks). • No data in pediatric patients. • <u>Hypersensitivity reactions</u>: In CS3, 2 (9%) subjects in the olezarsen 80 mg group discontinued because of hypersensitivity or flu-like reactions compared to none in placebo. There were no serious hypersensitivity reactions in CS3 or CS8 although 3 serious reactions were seen in the open-label extension trials. The onset of symptoms usually occur within minutes or same day of the injection. • <u>Decreases in Platelet Count</u>: Olezarsen treatment causes reductions in platelet counts. Platelet counts remain on average 5 to 15% below baseline. The incidence of bleeding events was low and similar across treatment groups. No olezarsen-treated subject in the FCS trial CS3 paused, reduced, or discontinued olezarsen dosing due to a bleeding AE. No olezarsen-treated subjects, to date, have reported a platelet count below $50 \times 10^9/L$.	• The most concerning risk is serious hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, chills, and myalgias. This risk is clinically monitorable by the healthcare provider. Olezarsen should be discontinued if serious hypersensitivity reactions occur. • The clinical impact of the drug-induced LDL-C and apoB increases in the FCS population is uncertain, but likely minimal in this population, because despite increases in LDL-C, the value remains low (i.e., $<70 \text{ mg/dL}$) for most study subjects. LDL-C is monitorable and can be mitigated with lipid-modifying therapy. • Small increases in liver enzymes occurred but the incidence of hepatic events was low and similar across treatment groups. This is described in Section 6.1 of the prescribing information (PI). A postmarketing requirement will assess further this potential liver signal in patients with severe hypertriglyceridemia along with enhanced pharmacovigilance for liver toxicity in the postmarket setting in patients with FCS. • The 80 mg dose of olezarsen, administered subcutaneously every month, was reasonably well-tolerated throughout these trials. Approximately 90% of patients with FCS in trial CS3 completed the one year trial. • All risks associated with olezarsen can be adequately addressed through labeling and no specific monitoring, beyond that necessary for the treatment and management of FCS, is recommended. Olezarsen is contraindicated in patients who have experienced serious hypersensitivity reactions with olezarsens. This finding is described in sections 4 and 5 of the PI. Common adverse reactions included injection site reactions, decreased platelet count, and arthralgia. Laboratory test abnormalities included decreases in platelet count and increases in glucose, liver enzymes, and low-density lipoprotein cholesterol (LDL-C). These laboratory changes were notable but did not lead to clinical adverse events and resolved with discontinuation of the drug.

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- Increases in Liver Enzymes: The incidence of hepatic events was low and similar across treatment groups. Olezarsen was associated with mean increases in ALT, AST, GGT within the first 3 months which stabilized, and remained within normal range. Liver enzymes returned towards baseline with discontinuation of olezarsen. In some subjects, increases in liver enzymes lead to discontinuation or interruption of study drug. There were no cases of Hy's Law, an indicator of drug-induced liver injury.
 - Dysglycemia: In trial CS3, average glucose and HbA1c values increased slightly more in the olezarsen treatment groups than placebo. Using an algorithmic FMQ for hyperglycemia consisting of adverse events, new antidiabetic medication, and laboratory values, a higher proportion of olezarsen-treated subjects without a medical history of diabetes at baseline (52%) versus placebo-treated subjects (35%) fulfilled at least one of the FMQ criterion, suggesting a safety signal for worsening glycemic control.
 - Injection site reactions (ISRs): ISRs, characterized primarily by erythema and discoloration, occur with olezarsen treatment. In CS3, ISRs occurred in 3 (14%) subjects in both the olezarsen 80 mg and 50 mg groups vs. 2 (9%) subjects in placebo group. None of the ISRs were serious, no subjects in FCS trials reduced study drug, withdrew from the trial, or required treatment of the ISR.
 - Changes in LDL-C and Apo B: Increases in LDL-C and apoB of approximately 50% from baseline were noted in the FCS population treated with olezarsen compared to a <1% increase in those treated with placebo. In contrast, in trial CS8 of subjects with moderate to high levels of triglycerides, LDL-C and apoB changes were smaller and were decreased in the olezarsen groups as compared to placebo.
 - Immunogenicity: Treatment with olezarsen results in development of treatment-emergent anti-drug antibodies in approximately 40% of treated subjects. No relationship between adverse events, including hypersensitivity events, and ADA status was seen in CS3 and CS8.
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Adverse events in CS3: Two (9%) subjects in the olezarsen 80 mg group compared to none in the placebo group discontinued treatment due to an AE. Adverse events that were increased in the 80 mg olezarsen treatment groups versus placebo were related to reductions in platelet count, injection site reactions, nasopharyngitis, erythema, and arthralgia. • Tolerability in CS3: Approximately 88% of subjects in the pooled olezarsen treatment group completed the one-year trial.	

^a FDA results from [Table 31](#)

^b FDA results from [Table 13](#)

^c FDA results from [Table 16](#), [Table 35](#)

Abbreviations: ADA, antidrug antibody; AE, adverse event; ALT, alanine aminotransferase; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; CI, confidence interval; FCS, familial chylomicronemia syndrome; FMQ, FDA medical query; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HTG, hypertriglyceridemia; ISR, injection site reaction; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; sHTG, severe hypertriglyceridemia; TG, triglycerides

2.2. Conclusions Regarding Benefit-Risk

The benefit of TG lowering, with the expectation of a reduction in risk for acute pancreatitis, in patients with FCS outweighs the potential risks in this population.

FCS is a rare genetic disorder of lipid metabolism characterized by excessive chylomicronemia and severe hypertriglyceridemia. The most serious complication is acute pancreatitis. Common, and sometimes debilitating, symptoms include episodic abdominal pain, fatigue, and depression. Other clinical manifestations include eruptive cutaneous xanthomas, lipemia retinalis, and hepatosplenomegaly. Current management of the disease is severe dietary restriction. There is no effective drug therapy, and there exists a high unmet need.

Olezarsen 80 mg once monthly effectively lowers TG levels in patients with FCS. TG lowering is considered a surrogate for reduction in the risk of acute pancreatitis. Numerically lower incidence of pancreatitis in patients assigned to FCS is supportive of the expected clinical benefit.

Trial CS3 was a 53-week, double-blind, placebo-controlled, randomized trial of adult subjects with FCS with fasting TG levels ≥ 880 mg/dL despite very low-fat (≤ 20 grams per day) diet and optimized lipid-lowering therapies. Olezarsen 80 mg administered every 4 weeks (as an add-on to background TG-lowering therapy) decreased TG at Month 6 by 44.5% compared to placebo. Over the 12-month treatment period, the numerical incidence of pancreatitis in subjects randomized to olezarsen 80 mg (one event experienced by one subject) was lower compared with the incidence in patients assigned to placebo (11 events experienced by seven subjects). Treatment discontinuation at one year was acceptable (14% in the olezarsen group versus 4% in the placebo group).

Even considering uncertainty around the magnitude of the benefit on acute pancreatitis based on reliance on a surrogate endpoint, the anticipated benefit clearly outweighs the risk in the FCS population.

The safety of olezarsen in patients with FCS was established by the clinical program. The most concerning risk is serious hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, chills, and myalgias. This risk is clinically monitorable and may be adequately communicated in the Contraindications and Warnings and Precautions section of the prescribing information. The risk for drug-induced liver injury was primarily seen in patients with moderate hypertriglyceridemia. The risk in patients with FCS is very low but an additional evaluation of this potential risk will be assessed further in postmarket requirements.

The clinical impact of the drug-induced LDL-C and apoB increases in the FCS population is uncertain but does not outweigh the benefit. Although LDL-C increased by approximately 50% and ApoB by approximately 12% compared to placebo, baseline values were very low (mean baseline LDL-C was 17 mg/dL in placebo and to 27 mg/dL in the 80 mg arms, while mean baseline total ApoB was 59.7 mg/dL and 58.4 mg/dL, respectively), thus the impact of these percentage increases is likely minimal. The absolute increase in these parameters was relatively low magnitude and remained within the normal range for most subjects. LDL-C is monitorable, and elevations can be mitigated with lipid-modifying therapy. Notably, LDL-C and ApoB decreased with olezarsen 80 mg versus placebo in the moderate and severe HTG populations in CS8 compared to placebo.

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Other adverse events, including decreases in platelet count, increases in liver enzymes, and increase in glucose are monitorable and may be communicated in the Adverse Reactions section of labeling.

Although the safety database is small, strengths include the placebo-controlled design, use of two doses to assess dose-response, the 1-year treatment duration, with additional longer-term exposure in the OLE, the low study drop-out rate, and small amount of missing data.

Modeling and simulation were used to bridge the Q4W regimen evaluated in clinical trials to the once monthly regimen proposed for the marketed product. There are not expected to be clinically meaningful differences between the to-be-marketed one monthly dosage and the Q4W regimen used in trials.

II. Interdisciplinary Assessment

3. Introduction

This review serves as the interdisciplinary assessment for NDA 218614, olezarsen sodium (Tryngolza) injection.

The Applicant (Ionis Pharmaceuticals, Inc.) is developing olezarsen as an adjunct to diet to reduce triglycerides (TG) in adults with familial chylomicronemia syndrome (FCS). The recommended dosage of olezarsen is 80 mg administered by subcutaneous (SC) injection once monthly.

FCS is a rare, autosomal recessive condition affecting 1 to 10 individuals in a million. Individuals with FCS have persistent elevated levels of TG, which increases their risk of pancreatitis, a potentially life-threatening consequence of this condition. The onset of symptoms in individuals with FCS usually occurs in childhood or adolescence and includes eruptive xanthomas, lipemia retinalis, episodic abdominal pain, and hepatosplenomegaly. A restrictive low-fat diet is the mainstay of therapy and is effective, but adherence is difficult. TG-lowering drugs, such as fibrates and fish oils, are largely ineffective in reducing TG in this population. There are no FDA-approved products for the treatment of FCS.

Olezarsen is an antisense oligonucleotide (ASO) inhibitor of apolipoprotein C-III (ApoC-III) production, covalently linked to a ligand containing three N-acetyl galactosamine (GalNAc) residues to enable delivery of the ASO to hepatocytes. Olezarsen causes degradation of *apoC-III* mRNA through binding to *apoC-III* mRNA, which results in a reduction of serum ApoC-III protein. ApoC-III is a key regulator of TG metabolism via lipoprotein lipase (LPL) dependent and independent mechanisms. By reducing ApoC-III production, olezarsen decreases the negative effect of ApoC-III on TG clearance, thereby lowering TG levels. The lipid biomarker TG has historically been used as a surrogate for reduction in risk of pancreatitis and the basis of full approval for TG-lowering drugs in patients with hypertriglyceridemia (HTG) (TG $\geq$ 500 mg/dL).

Olezarsen shares the same nucleotide sequence as its parent drug, volanesorsen. Volanesorsen received a conditional marketing authorization for patients with FCS at high risk for pancreatitis by the European Medical Agency in 2019 but received a complete response letter from the Agency in 2018, (b) (4)

(EMA 2019). Olezarsen is differentiated from volanesorsen by its conjugation to GalNAc, which permits a different therapeutic dosing regimen of olezarsen (80 mg administered SC every 4 weeks [Q4W]) compared to volanesorsen (300 mg administered SC once per week [Q1W]).

The IND application for olezarsen was opened in December 2017, with a phase 2 trial of individuals with moderately elevated TG (TG 200 to 500 mg/dL) with established coronary artery disease (Trial ISIS 678354-CS2). Following the primary analysis of the phase 2 trial, the Applicant elected to focus on the study populations of FCS and severe hypertriglyceridemia (sHTG) (TG $\geq$ 500 mg/dL). Multiple interactions between the Applicant and Division have occurred to discuss the Applicant's development plans for FCS, including Type C meetings in

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July 2020 and August 2022, advice letters following review of phase 3 protocols, statistical analysis plan (SAP), integrated summary of safety, and a pre-NDA meeting in December 2023.

Olezarsen is a new molecular entity and is not currently marketed in the United States. Olezarsen would be first-in-class for the treatment of FCS, for which there are no FDA-approved therapies. Olezarsen received fast track designation in January 2023, breakthrough therapy designation in February 2024, and priority review for this NDA submission. Refer to Section [12](#) for a detailed summary of the regulatory history.

Trial ISIS 678354-CS3, the pivotal trial in this submission, was conducted to evaluate the efficacy and safety of olezarsen as compared to placebo in 66 adults with genetically confirmed FCS. The trial was designed as a double-blind, placebo-controlled, 53-week trial. Eligible study subjects were randomized to either olezarsen 50 mg, olezarsen 80 mg, or placebo administered SC Q4W. The primary efficacy endpoint was percentage change in fasting TG from baseline to Month 6 (average of Week 23, 25, and 27 assessments). Other evaluations included assessment of the effect of olezarsen on non-HDL-C concentrations and adjudicated acute pancreatitis (AP) event rates. Safety and tolerability assessments included adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), use of concomitant medications, and independently adjudicated event rate of major adverse cardiovascular events (MACE) for olezarsen compared with placebo.

The safety and confirmatory evidence of effectiveness of olezarsen in patients with HTG was provided with data from phase 2b Trial ISIS 678354-CS8, and other trials in the olezarsen clinical development program. Trial CS8 was a multicenter, randomized, double-blind, placebo-controlled trial evaluating olezarsen 50 mg or olezarsen 80 mg administered Q4W as an SC injection for 1 year in 154 subjects with HTG and atherosclerotic cardiovascular disease (established or at increased risk for), and/or with sHTG. The primary efficacy endpoint was the percent change in fasting TG from baseline at Month 6, which was defined as the average of Weeks 25 and 27, compared with the placebo group. Safety assessments were similar to those of Trial CS3.

The review team identified three review issues relevant to the evaluation of benefit (Section [6.3](#))

- Confirmation of efficacy of TG reduction of the 80 mg dose in Trial CS3
- (b) (4)
- Confirmation of the reduction in pancreatitis events in Trial CS3

At the start of the review process, several potential risks were identified for olezarsen based on prior knowledge of both olezarsen and volanesorsen. These risks (or potential risks) were multidisciplinary and included concerns such as hypersensitivity reactions, thrombocytopenia, hepatic-related or renal-related events, dysglycemia, and the bridging of the vial and autoinjector (commercial product), as the 90% confidence interval (CI) for maximum plasma concentration (C_{max}) for the 80 mg dose is outside the standard upper CI limit of 80 to 125%.

At the conclusion of this NDA review, the team identified the following risks that were important to highlight in the overall benefit/risk assessment (please refer to Section [7.7](#)):

- Hypersensitivity reactions
- Platelet reductions and bleeding events
- Hepatic-related AEs
- Dysglycemia
- Injection site reactions (ISRs)
- Changes in low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (ApoB)

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

The review team identified the key review issues, listed in Sections [3.1.1](#) and [3.1.2](#) below, relevant to the evaluation of benefit and risk, respectively. A detailed assessment of these benefit and risk issues can be found in Sections [6.3](#) and [7.7](#), respectively.

3.1.1.1. Efficacy of Triglyceride Reduction of 80 mg Olezarsen in Trial CS3 in the FCS Population

The review team concluded that the results of the primary endpoint of TG reduction of olezarsen 80 mg dose was statistically significant compared to placebo and was sufficient to establish the efficacy of olezarsen 80 mg dose for TG reduction in the FCS population.

3.1.1.2. (b) (4)

 (b) (4)

3.1.1.3. Acceptability of the Secondary Endpoint of Acute Pancreatitis Risk Reduction

Trial CS3 assessed key secondary endpoints of a reduction in prospectively adjudicated AP; it is the first outcome trial submitted to the FDA to measure adjudicated AP in an HTG population. The nominal finding of a reduction in the rate of AP is consistent with the pathophysiology that links elevated levels of TG with AP and the reduction of TG with a subsequent reduction in AP.

3.1.1.4. Adequacy of the Confirmatory Evidence in Trial CS8 in the Severe and Moderate Hypertriglyceridemic Populations

The following lines of evidence constitute adequate confirmatory evidence of treatment benefit: (1) well-understood underlying disease pathophysiology; (2) targeted mechanism of action of olezarsen; (3) evidence of drug effect on a pharmacologically relevant biomarker; and (4) evidence of exposure-response on the biomarker.

The review team established that there is adequate confirmatory evidence to generate substantial evidence of effectiveness (SEE) with Trial CS8, a phase 2 trial in severe and moderate HTG populations. For a detailed discussion, refer to Section [6.3.4](#).

3.1.1.5. Confirmation of Other Lipoproteins and Parameters in Trial CS3 in the FCS Population

The lipid parameters LDL-C, non-HDL-C, total ApoB and ApoC-III levels were confirmed by the statistical team. These changes in the lipid profile (LDL-C, non-HDL-C, and total ApoB) are expected based on the lipid metabolism pathway and do not alter the favorable benefit-risk profile of olezarsen 80 mg of reducing TG and the risk of AP. The reduction of ApoC-III confirmed the mechanism of action of olezarsen.

3.1.2. Key Safety Review Issues

3.1.2.1. Hypersensitivity Reactions

Hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, chills, and myalgias, requiring medical treatment have occurred in patients treated with olezarsen.

3.1.2.2. Platelet Reductions and Bleeding Events

Olezarsen can cause reductions in platelet count, including reductions below the lower limit of normal. No olezarsen-treated patient with FCS had severe thrombocytopenia, defined as a platelet count $<50,000/\text{mm}^3$. There were no major bleeding events associated with a low platelet count. Overall, the proportion of patients experiencing a bleeding adverse event was similar across treatment groups.

3.1.2.3. Increases in Liver Enzymes

Increases from baseline in liver enzymes within the normal range were observed with olezarsen treatment in the FCS population. The incidence of hepatic events was low and similar across treatment groups. In some subjects, increases in liver enzymes lead to discontinuation or interruption of study drug. There were no cases of Hy's Law, an indicator of drug-induced liver injury.

3.1.2.4. Dysglycemia

Small increases in average values in fasting glucose and HbA1c over time were observed with olezarsen treatment in the FCS population. Using an algorithmic FDA Medical Dictionary for Regulatory Activities Query (FMQ) for hyperglycemia consisting of adverse events, new antidiabetic medication, and laboratory values, a higher proportion of olezarsen-treated subjects without a medical history of diabetes at baseline (52%) versus placebo-treated subjects (35%) fulfilled at least one of the FMQ criterion, suggesting a safety signal for worsening glucose metabolism.

3.1.2.5. Injection Site Reactions

Injection site reactions (ISRs), characterized primarily by erythema and discoloration, occur with olezarsen treatment. In CS3, ISRs occurred in 3 (14%) subjects in both the olezarsen 80 mg and 50 mg groups vs. 2 (9%) subjects in placebo group. None of the ISRs were serious, no subjects in FCS trials reduced study drug, withdrew from the trial, or required treatment of the injection site reaction (ISR).

3.1.2.6. Increase in LDL-C

Increases in LDL-C and total apolipoprotein B (apoB) were observed in the FCS population treated with olezarsen compared to those treated with placebo. Despite increases in LDL-C, the value remained low (i.e., <70 mg/dL) for most patients.

3.1.2.7. Imbalance in Cardiovascular Events

In the olezarsen clinical development program there was a higher number of deaths, serious cardiac events, and adjudicated MACE with olezarsen treatment compared to placebo treatment. Most of the serious cardiac events and MACE occurred in a non-FCS population with underlying cardiovascular comorbidities. The number of MACE and duration of exposure is too small to provide a definitive causality assessment for olezarsen. At this time there is no clear signal of cardiovascular harm in the FCS population.

3.1.2.8. Immunogenicity

Treatment with olezarsen results in development of treatment-emergent antidrug antibodies (ADA) in approximately 40% of treated subjects. No relationship between adverse events, including hypersensitivity events, and ADA status was seen in CS3 and CS8.

3.2. Approach to the Clinical Review

The primary evidence of efficacy and safety for olezarsen for the proposed indication of an adjunct to diet to reduce TG in adults with FCS is provided by a single adequate and well-controlled trial conducted in the United States, Canada, the United Kingdom, and Europe (Trial CS3; ISIS 678354-CS3). CS3 is a randomized, double-blind, placebo-controlled phase 3 trial. Refer to Sections [6.2.2](#) and [7.6.2](#) for additional details. In addition to Trial CS3, a trial conducted

in the United States and Canada (Trial CS8; ISIS 678354-CS8) provided confirmatory evidence of olezarsen effectiveness to substantiate the results of CS3 and provided supportive safety data. CS8 is a randomized, double-blind, placebo-controlled phase 2b trial. Refer to Sections [6.2.3](#) and [7.6.3](#) for additional details. Recommendations from FDA during protocol development were, for the most part, incorporated into the trial design for CS3 and CS8.

Additional supportive information was provided by the open-label extension (OLE) of the CS3 pivotal trial (ISIS 678354-CS13) and the OLE of the CS7 trial (ISIS 678354-CS7); the latter trial in subjects previously administered volanesorsen. These four trials provide the basis of the benefit-risk assessment for olezarsen in patients diagnosed with FCS. In general, these trials included similar subject populations (FCS in CS3, CS13, and CS7; moderate/severe HTG in CS8), dosage regimens for olezarsen, as well as primary endpoint definitions and timing of assessments in CS3 and CS8. The Applicant asserts that all of the trials were conducted according to the International Council for Harmonisation tripartite guideline on Good Clinical Practice. Refer to Section [7.5](#) for additional details.

Additional supportive safety and efficacy information from Trial CS2 (ISIS 678354-CS2), which enrolled subjects with HTG with or at high risk for cardiovascular disease (CVD), was also submitted. This trial used smaller doses than the proposed marketed dosage of 80 mg monthly. The Applicant provided additional information to support the applicability of the data from the non-U.S. sites to the U.S. population and provided full clinical study reports and data sets for all five trials. Although olezarsen is not yet commercially available in any country, volanesorsen shares the identical oligonucleotide sequence as olezarsen and is approved outside of the United States. Given their similarities, the safety for volanesorsen was reviewed during the previous FDA review for volanesorsen (NDA 210645) as well as the global marketed experience of volanesorsen.

[Table 3](#) provides an overview of these five clinical trials.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Olezarsen

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
ISIS 678354-CS3 (NCT04568434)	Genetically confirmed FCS, fasting TG ≥ 880 mg/dL	Control type: PC Randomization: Randomly assigned to Cohort A (50 mg) or Cohort B (80 mg) in a 1:1 ratio; each cohort was further randomized 2:1 to either the olezarsen dose for the cohort or placebo Blinding: DB Biomarkers: TG Innovative design features: N/A	Drug: olezarsen injection SC, Q4W Dosage: olezarsen 50, olezarsen 80 mg, or placebo Number treated: 66 Duration (quantity and units): 53 wk	Primary: mean percent change in fasting TG from baseline at Month 6 (average of Weeks 23, 25, and 27): first in the olezarsen 80 mg group, then in the olezarsen 50 mg group. Secondary: % change in fasting TG from baseline to Month 12 between olezarsen 80 mg group and pooled placebo	Planned: 60 Randomized: 66	29 sites enrolled at least 1 subject: US (9), Canada (3), EU (16), UK (1)

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Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
ISIS 678354-CS8 (NCT05355402)	HTG, Established or Increased Risk of ASCVD, and/or sHTG	Control type: PC Randomization: Randomly assigned to Cohort A (50 mg) or Cohort B (80 mg) in a 1:1 ratio; each cohort was further randomized 3:1 to either the olezarsen dose for the cohort or placebo Blinding: DB Biomarkers: TG Innovative design features: N/A	Drug: olezarsen injection SC, Q4W Dosage: olezarsen 50, olezarsen 80 mg, or placebo Number treated: 154 Duration (quantity and units): 53 wk	Primary: mean percent change in fasting TG from baseline at Month 6 (average of Weeks 25 and 27): first in the olezarsen 80 mg group, then in the olezarsen 50 mg group. Secondary: 80 mg: % change in fasting TG from baseline at Month 12	Planned: 152 Randomized: 154	28 sites: US (21), Canada (7)
ISIS 678354-CS2	HTG and Established or at High Risk for CVD	Control type: PC Randomization: 1:1:1:1 ratio to 1 of 4 parallel-dose cohorts (Cohorts A, B, C or D). Within each cohort, randomized in 4:1 ratio to ISIS 678354/olezarsen or placebo. Blinding: DB Biomarkers: TG Innovative design features: N/A	Drug: olezarsen Dosage: olezarsen 10 mg Q4W; olezarsen 50 mg Q4W; olezarsen 15 mg Q2W; olezarsen 10 mg QW; or placebo Number treated: 114 Duration (quantity and units): 52 wk	Primary: % change in fasting TG from baseline at Month 6 Secondary: % change from baseline in apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I	Planned: 100 Randomized: 114	41 sites: US (34), Canada (7)

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Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
ISIS 678354-CS13 (NCT05130450)	FCS	Control type: None Randomization: None Blinding: OL Biomarkers: TG Innovative design features: LTE	Drug: olezarsen Dosage: olezarsen 80 mg (Dose reduction to 50 mg allowed if needed) SC; Q4W Number treated: 54 Duration (quantity and units): 157 wk	Primary: Safety and tolerability Secondary: Percent change in fasting TG from baseline at Month 6 (average of Weeks 23, 25, and 27)	Planned: 60 Randomized: 54	23 sites: US (6), Canada (3), and 14 sites in Europe (France, Italy, Netherlands, Norway, Portugal, Slovakia, Spain, and Sweden).
ISIS 678354-CS7 (NCT05185843)	FCS	Control type: None Randomization: None Blinding: OL Biomarkers: TG Innovative design features: Switch	Drug: olezarsen (previously treated with volanesorsen) Dosage: olezarsen 80 mg (Dose reduction to 50 mg allowed if needed) SC; Q4W Number treated: 24 Duration (quantity and units): 157 wk	Primary: Safety and tolerability Secondary: Percent change in fasting TG from baseline at Week 53	Planned: 24 Randomized: 24	12 sites: US (5), Canada (6), Sweden (1).

Source: Reviewer.

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

² If no randomization, then replace with "Actual Enrolled."

Abbreviations: Apo, apolipoprotein; ASCVD, Atherosclerotic Cardiovascular Disease; DB, double-blind; EU, European Union; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; LTE, long-term extension; N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; Q2W, every two weeks; Q4W, every 4 weeks; SC, subcutaneous; sHTG, severe hypertriglyceridemia; TC, total cholesterol; TG, triglycerides; wk, week(s); mo, month(s); y, year(s); UK, United Kingdom; US, United States;

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how SEE was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant’s proposed indication if the application received a complete response):

TRYNGOLZA is indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).

2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

Adequate and well-controlled clinical investigation(s):

- Two or more adequate and well-controlled clinical investigations, **OR**
 One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- One adequate and well-controlled clinical investigation and confirmatory evidence ([May 1998](#); [December 2019](#); [September 2023](#))

OR

- Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

3. Complete response, if applicable

- SEE was established
 SEE was not established (*if checked, omit item 2*)

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		Section Where Discussed, if Applicable
Check if Submitted	Type of Data	
Clinical Outcome Assessment Data Submitted in the Application		

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcomes (PROs) • Familial Chylomicronemia Syndrome Symptoms and Impacts Scale (FCS-SIS) • FCS Diet Questions for Daily Diary • Patient-Reported Outcome Measurement Information System (PROMIS) Adult Short Form v1.1 – Pain Interference 8a • PROMIS 29+2 Profile v2.1 (PROPr) • PROMIS Short Form v2.0 – Cognitive Function 4a • Patient Global Impression of Severity (PGIS) • Patient Global Impression of Change (PGIC)	The PROs and COAs are discussed in Section 16.3 .
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	See DCOA Review for a summary of the findings of the exit interview report.
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	See DCOA Review
☒	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Abbreviations: COA, clinical outcome assessment; DCOA, Division of Clinical Outcome Assessment

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

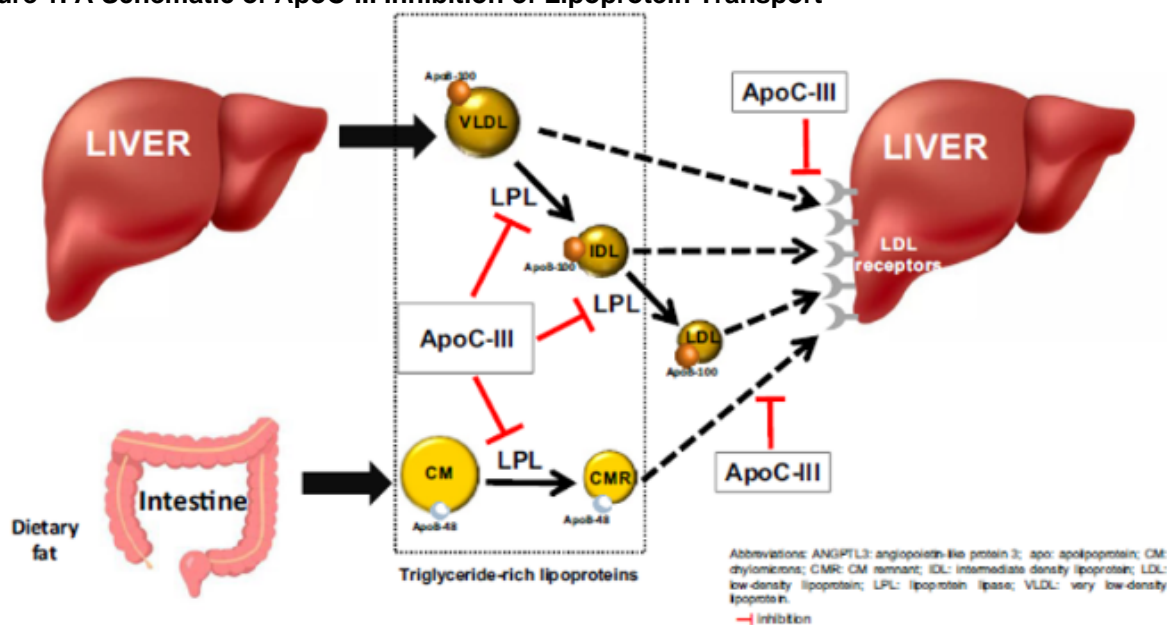
5.1. Nonclinical Assessment of Potential Effectiveness

Olezarsen (ISIS 678354) is an *apoC-III* mRNA-directed ASO proposed for an indication as an adjunct to diet to reduce TG in adults with FCS. Olezarsen is comprised of the active ASO component (identical to volanesorsen, which is marketed outside the United States) that is covalently attached to triantennary N-acetyl galactosamine (GalNAc3) via a (b) (4)

linker to form an ASO-GalNAc conjugate. The ASO portion binds to *apoC-III* mRNA and the GalNAc3 portion targets the hepatocyte-specific asialoglycoprotein receptor, which is expressed abundantly on the hepatocyte cell surface. After internalization, the GalNAc3 and linker are cleaved to release the free ASO. The ASO portion of olezarsen binds to the 3' untranslated region of *apoC-III* mRNA and results in ribonuclease H1-mediated degradation, preventing the production of ApoC-III protein.

FCS is a rare, serious, autosomal recessive inherited disease of lipid metabolism characterized by severely impaired LPL activity and extremely high levels of plasma TG carried primarily by chylomicrons (resulting in HTG and hyperchylomicronemia). Olezarsen targets *apoC-III* mRNA and reduces expression of ApoC-III protein, a key regulator of plasma TG levels (Figure 1), leading to increased TG LPL activity, hepatic uptake of TG-rich lipoproteins, and hepatic lipase activity. The increased clearance of plasma TG (as chylomicrons and very low-density lipoprotein particles) would be expected to significantly reduce plasma TG and chylomicron levels in individuals with FCS.

Figure 1. A Schematic of ApoC-III Inhibition of Lipoprotein Transport



Source: Figure modified from (Ward et al. 2022)

Abbreviations: ANGPTL3, angiotensin-like protein 3; apoB, apolipoprotein B; apoC-III, apolipoprotein C-III; CM, chylomicron; CMR, CM remnant; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein

The pharmacological activity of olezarsen was characterized in vitro in primary human hepatocytes (HepatoPac®) and primary hepatocytes of transgenic mice expressing the human *apoC-III* gene. Olezarsen produced a concentration-dependent reduction of *apoC-III* mRNA with an IC_{50} of 0.18 μ M and a maximal efficacy of 82% in human hepatocytes, and reduced *apoC-III* mRNA levels in transgenic mouse hepatocytes with an IC_{50} of 0.012 μ M and maximal efficacy of 89%.

Studies with olezarsen or a mouse-specific surrogate were conducted in several animal models. In wild-type mice, a mouse-specific *apoC-III* surrogate ASO was used (ISIS 838707, a murine

GalNac3-conjugated version), due to the divergence in sequence between mouse and human *apoC-III* mRNA. In wild-type mice, using the surrogate, liver *apoC-III* mRNA expression and plasma TG levels were reduced by up to 88% and 76%, respectively, compared to control mice following 6-week treatment with olezarsen. Studies were also conducted in human *apoC-III* transgenic mice. In the transgenic mice, a single dose of olezarsen up to 10 mg/kg resulted in dose-dependent reductions in liver *apoC-III* mRNA by up to 77%, and reduced plasma ApoC-III protein and plasma TG levels by up to 87%. Olezarsen exhibits full complementarity to the *apoC-III* mRNA transcript of humans and cynomolgus monkeys. In monkeys administered olezarsen once weekly for up to 39 weeks, there were dose-dependent reductions in liver *apoC-III* mRNA of up to 90% and reductions in plasma ApoC-III protein of up to 77%. Minimal effects on plasma TG levels were seen in monkeys given olezarsen, which was likely because chow-fed monkeys have very low plasma TG levels at baseline. Overall, these animal models demonstrated dose and time-dependent reductions in hepatic *apoC-III* mRNA, plasma ApoC-III protein, and (in rodents) plasma TG levels (see Section 13 for further details). The observed effects were consistent with the expected pharmacological properties of the compound. Results from these animal models provide reasonable proof-of-concept that supported the initiation of human trials as assessed using a clinically translatable and monitorable pharmacological endpoint, plasma TG.

Of note, a robust series of nonclinical pharmacology studies were previously conducted with volanesorsen, the unconjugated active antisense oligonucleotide component of olezarsen, which lacks the GalNac moiety but is otherwise structurally identical. Volanesorsen has not received marketing approval in the United States, but the nonclinical studies with the active component are considered relevant and were cross-referenced by the Applicant to the current NDA. Olezarsen and volanesorsen demonstrate a similar pharmacologic profile (sequence identical and specific knockdown of *apoC-III* mRNA in monkeys and humans) and differ primarily in their pharmacokinetic and tissue distribution profiles. Olezarsen is specifically distributed to the liver and therefore a more rapid liver uptake and lower nominal doses of olezarsen were theoretically achievable compared to volanesorsen, which lacks GalNac.

There was no evidence of off-target activity against other mRNA or downstream protein targets. Olezarsen is not an inhibitor or an inducer of major drug-metabolizing cytochrome P450 enzymes nor is it a substrate or inhibitor of various drug transporters. The established pharmacologic class for olezarsen should be consistent with prior members of the same drug class, i.e., “*Olezarsen is an APOC-III-directed ASO indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)*”.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	APOC-III-directed antisense oligonucleotide (ASO)
Mechanism of action	Olezarsen is a 2'-O-methoxyethyl (2'-MOE) chimeric ASO covalently bound to triantennary N-acetyl galactosamine (GalNac3), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor. The ASO portion of olezarsen

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Characteristic	Drug Information						
	is the parent drug, volanesorsen, and is designed to bind to the human apoC-III messenger ribonucleic acid (mRNA). Olezarsen causes degradation of apoC-III mRNA through selective binding to apoC-III mRNA, which results in a reduction of serum apoC-III protein. Studies suggest that apoC-III regulates both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins.						
Active moieties	Olezarsen						
QT prolongation	At a dose 1.5 times the maximum recommended dose for Tryngolza, clinically significant QTc interval prolongation was not observed.						
General Information							
Bioanalysis	Plasma and urine concentrations of olezarsen were determined by validated hybridization electrochemiluminescence (ECL) and partially validated enzyme-linked immunosorbent assay (ELISA) methods. These methods assess the total concentration of full-length ASOs, including fully conjugated, partially conjugated (i.e., olezarsen with 1, 2, or 3 GalNAc sugar deletions), and unconjugated olezarsen (volanesorsen). The performance of bioanalytical methods and the results of quantification were acceptable.						
Healthy subjects versus patients	No apparent differences in the PK parameters were observed following multiple subcutaneous administrations of 80 mg olezarsen once every 4 weeks between patients with FCS and healthy volunteers.						
Drug exposure at steady state following the therapeutic dosing regimen (80 mg once monthly)	<table border="1"> <thead> <tr> <th>Parameter</th> <th>Mean ± SD</th> </tr> </thead> <tbody> <tr> <td>AUC_{tau}</td> <td>7440 ± 3880 ng*h/mL</td> </tr> <tr> <td>C_{max}</td> <td>883 ± 662 ng/mL</td> </tr> </tbody> </table>	Parameter	Mean ± SD	AUC _{tau}	7440 ± 3880 ng*h/mL	C _{max}	883 ± 662 ng/mL
Parameter	Mean ± SD						
AUC _{tau}	7440 ± 3880 ng*h/mL						
C _{max}	883 ± 662 ng/mL						
Range of effective dose(s) or exposure	The 80 mg Q4W was shown to be effective in reducing TG levels in subjects with FCS in the Phase 3 Study ISIS 678354-CS3.						
Maximally tolerated dose or exposure	A maximum tolerated dose was not determined. A suprathreshold dose of 120 mg was studied as a single dose in Phase 1 Study ISIS-678354-CS1.						
Dose proportionality	In Study ISIS 678354-CS1, olezarsen exposure (C _{max} and AUC) increased in a dose-proportional manner at doses ranging from 10 to 120 mg (slope of 1.35 for C _{max} and 1.27 for AUC using linear regression analyses of the log-transformed data).						
Accumulation	No accumulation of olezarsen C _{max} and AUC was observed in repeated dosing (once every 4 weeks). Accumulation in C _{trough} was observed with once every 4 weeks administration in both healthy volunteers and patients with FCS. Based on the population PK model, the predicted accumulation in C _{trough} is 2.3-fold.						
Time to achieve steady state	Steady-state trough in patients with FCS appeared to be reached by Day 169 consistent with the apparent terminal elimination half-life of approximately 30 days in plasma						
Bridge between to-be marketed and clinical trial formulations	The intended commercial drug product presentation of prefilled syringe with an autoinjector is supported by the BE study (Study ISIS 678354-CS20)						
Absorption							
Bioavailability	The absolute bioavailability after subcutaneous administration of olezarsen was not determined.						
T _{max}	Following subcutaneous administration, the T _{max} for olezarsen is approximately 2 hours post dose, based on population estimates.						
Distribution							
Volume of distribution	The population estimates for the apparent central volume of distribution is 91.9 L and the apparent peripheral volume of distribution is 2960 L.						
Plasma protein binding	Protein binding of olezarsen > 99%						
Drug as substrate of transporters	Olezarsen was not a substrate for major drug transporters in vitro.						

Characteristic	Drug Information
Elimination	
Mass balance results	A mass balance study was not conducted due to the risk of prolonged residence time in liver. Urinary excretion of total full-length olezarsen within the first 24 hours represented a small fraction of the administered dose (< 1% of administered dose) in healthy volunteers. The low renal clearance over the first 24 hours supports the hypothesis that the initial plasma clearance is the result of rapid tissue uptake, not excretion. The ultimate elimination of unconjugated olezarsen is likely a combination of slow nuclease metabolism within tissues and subsequent excretion of shortened metabolites (as well as any remaining full-length oligonucleotide) into urine.
Clearance	Population PK model estimated apparent clearance was 13.5 L/h.
Half-life	The terminal elimination half-life is approximately 30 days.
Metabolic pathway(s)	The ASO-moiety of olezarsen (volanesorsen) is metabolized by endo- and exonucleases in tissues to shorter oligonucleotide metabolites. Oligonucleotides like olezarsen are not substrates for the classic CYP metabolic pathways.
Intrinsic Factors and Specific Populations	
Body weight	While there was a clear trend of declining exposure with increasing body weight for C _{max,ss} and AUC _{tau,ss} , no such apparent trend was identified for C _{trough,ss} . Considering steady-state apoC-III and TG reductions (percent change-from-baseline) were similar across different body weight groups, the impact of body weight on olezarsen PK was not considered clinically meaningful, and a fixed dose of 80 mg monthly is appropriate, regardless of body weight.
Age	Age (adults aged < 65 years [N = 223], 65 to 74 years [N = 41], and ≥ 75 years [N = 8]) was not identified as a statistically significant covariate in the population PK analysis.
Renal impairment	No dosage adjustment is needed for patients with mild or moderate impairment of renal function. Olezarsen was not studied in patients with severe renal impairment.
Hepatic impairment	No dosage adjustment is needed for patients with mild hepatic impairment. Olezarsen was not studied in patients with moderate or severe hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Olezarsen did not show any direct or time-dependent inhibition of any of the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) in vitro at clinically relevant concentrations. Olezarsen did not induce CYP1A2, 2B6 or 3A4 at clinically relevant concentrations.
Inhibition/induction of transporter systems	Olezarsen was not a substrate or an inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BSEP, BCRP, or P-gp.
Immunogenicity	
Bioanalysis	The ADA assay's ability to detect anti-olezarsen antibodies in the presence of circulating olezarsen (drug tolerance) was determined to be 39.1 ng/mL of antibody in the presence of up to 4000 ng/mL of olezarsen which is found to be acceptable. OPQR reviewed the Applicant's ADA assay and confirmed that it is suitable to detect ADAs against olezarsen.
Incidence	With duration of treatment up to 53 weeks, treatment-emergent ADAs against olezarsen were detected in 38.1% (8/21) of patients in the 50 mg olezarsen group, 45.5% (10/22) of patients in the 80 mg olezarsen group in Study ISIS 678354-CS3. ADAs to olezarsen were not characterized for neutralizing activity.

Characteristic	Drug Information
Clinical impact	The presence of ADAs did not affect olezarsen plasma C _{max} but increased AUC and C _{trough} . Although anti-drug antibody development was not found to affect the pharmacodynamics, safety, or efficacy of Tryngolza in these patients, the available data are limited to make definitive conclusions.

Source: FDA reviewer

Abbreviations: ADA, antidrug antibody; ASO, antisense oligonucleotide; AUC, area under the concentration-time curve; AUC_{0-12h,ss}, area under the concentration-time curve as of the last measured time point at steady state; BCRP, breast cancer resistance protein; BE, bioequivalence; BSEP, bile salt export pump; C_{max}, maximum plasma concentration; C_{max,ss}, maximum plasma concentration at steady state; C_{trough}, trough plasma concentration; CYP, cytochrome P450; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; EPC, established pharmacologic class; FCS, familial chylomicronemia syndrome; GalNac3, N-acetyl galactosamine; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetics; SD, standard deviation; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Proposed Olezarsen Dosage Regimen

The Applicant's proposed dosage of Tryngolza for the proposed indication is 80 mg administered by SC injection once monthly (Q1M).

Missed Dose

Administer Tryngolza as soon as possible after a missed dose. Resume dosing at monthly intervals from the date of the most recently administered dose.

6.1.2. Dose Selection Rationale for Clinical Trials

The 50 mg and 80 mg doses of olezarsen Q4W were selected for both the pivotal Trial ISIS 678354-CS3 and the confirmatory efficacy Trial ISIS 678354-CS8 based on the pre-clinical data and the pharmacokinetic (PK), pharmacodynamic (PD), and safety analyses from the Phase 1 study in healthy volunteers with HTG (ISIS 678354-CS1) and the results of the Phase 2 study in patients with atherosclerotic cardiovascular disease (ASCVD) and HTG (ISIS 678354-CS2).

A pooled analysis of safety for the Phase 1 and Phase 2 clinical studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (Phase 1: 10 to 120 mg single doses, 15 or 30 mg per week for 6 weeks, and 60 mg Q4W for 13 weeks; Phase 2: 10 mg or 50 mg Q4W, 15 mg Q2W, and 10 mg Q1W, all for at least 6 months and up to 1 year).

Considering that patients with FCS have extremely high TG levels (often >2000 mg/dL), and that the targeted TG range for these patients was <880 mg/dL, a maximal TG reduction over 70% was considered optimal for olezarsen to prevent the risk of AP. Population PK/PD model-based simulations for a population of patients with FCS predicted a 70% reduction in TG levels and an 86% reduction in ApoC-III levels with a dosing regimen of 80 mg Q4W, which was selected as the highest dose tested in this study. The 50 mg Q4W dose of olezarsen was expected

to produce a 64% TG lowering and a 79% ApoC-III lowering from baseline and was included in the study to evaluate dose-response.

Patients with FCS require chronic treatment, and therefore a Q4W dosing regimen may provide advantages over weekly dosing in terms of convenience and compliance for patients.

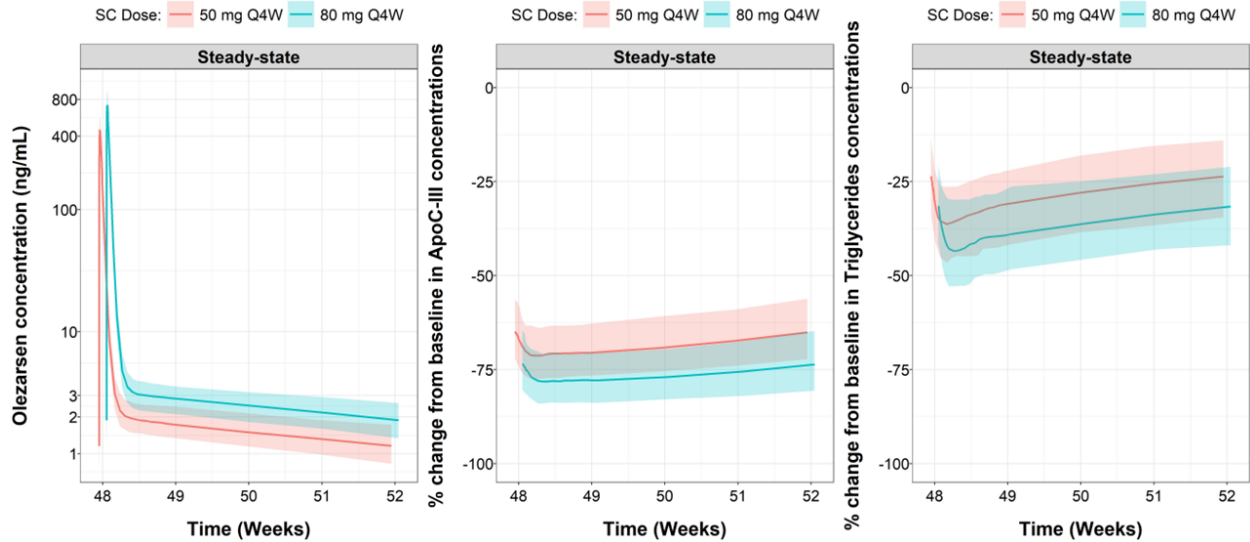
6.1.3. Exposure-Response Relationship for Efficacy and Safety

Evaluation of the Proposed Dosage Regimen

The dosing regimen is supported by the favorable benefit-risk profiles in patients with FCS (Trial ISIS 678354-CS3) and efficacy and safety profiles in patients with HTG and ASCVD/high-risk for ASCVD or with sHTG (Trial ISIS 678354-CS8, see Section 6.2). In ISIS 678354-CS3, the olezarsen 80 mg group had a greater placebo-adjusted mean percent decrease in fasting TG from baseline compared with the 50 mg group at Month 6 (44.5% for the 80 mg group vs. 21.5% for the 50 mg group) and at Month 12 (61.4% vs. 43.2%, see Section 6.2.2.6 for details). For the primary endpoint of mean percent decrease in fasting TG levels from baseline at Month 6, the decrease for the 80 mg group compared with the placebo group was statistically significant ($p=0.0015$), but the same comparison for the 50 mg group and the placebo group did not reach statistical significance ($p=0.1153$). Consistent with the mechanism of action of olezarsen, the 80 mg group had a greater placebo-adjusted mean percent decrease in ApoC-III levels from baseline compared with the olezarsen 50 mg group at Month 6 (73.69% vs. 65.48%), and at Month 12 (81.28% vs. 77.06%). Consistent with the results observed in ISIS 678354-CS3, a greater mean percent decrease from baseline in TG levels and ApoC-III levels in the 80 mg group compared with the 50 mg group was also observed in ISIS 678354-CS8. The adjudicated AP event rates were the same for the 80 mg group (one [4.5%] patient experienced one event) and 50 mg group (one [4.8%] patient experienced one event).

In addition, population PK and exposure-response modeling and simulation were conducted to support the proposed dosing regimen. According to the exposure-ApoC-III and exposure-TG modeling and simulation, 50 mg and 80 mg olezarsen administered Q4W are estimated to achieve, at steady-state exposure and the end of the dosing interval, a median percent reduction from baseline in ApoC-III of 64.7% versus 73.5% (for 50 mg versus 80 mg), and a median percent reduction from baseline in TG of 23.4 versus 29.4%, in patients with FCS. [Figure 2](#) shows a trend towards a marginally higher percentage change from baseline (CFB) in ApoC-III and TG for the 80 mg compared to the 50 mg doses, with overlapping 95% CIs for the percent CFB in TG concentrations.

Figure 2. Predicted Olezarsen, ApoC-III, and TG Concentration-Time Profiles for 50 mg and 80 mg Q4W



Source: FDA reviewer.

Note: Solid lines: median of the simulated observations. Shaded areas: 95% CI of the simulated median observations obtained from Monte-Carlo simulations (1000 replicates of a virtual FCS population with the same demographic characteristics as study ISIS 678354-CS3 (n=43)) and ADA negative status.

Abbreviations: ADA, antidrug antibody; Apo, apolipoprotein; CI, confidence interval; FCS, familial chylomicronemia syndrome; Q4W, every four weeks; SC, subcutaneous; TG, triglycerides

The relationship between olezarsen exposure metrics and the maximum reduction in platelet count (from merged studies ISIS 678354-CS3 and -CS8) is relatively shallow, with most patients experiencing less than grade 1 thrombocytopenia, and most patients with highest maximum decrease in platelets counts having no ADA or maximum ADA titer lower or equal to 800 ([Figure 65](#)).

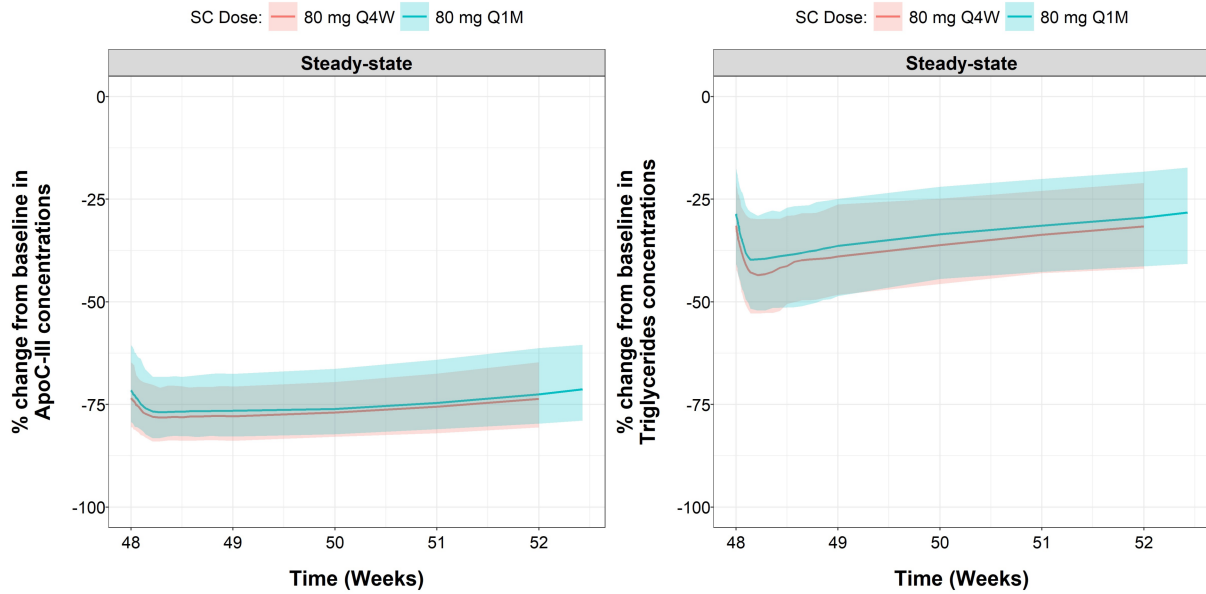
Dosing Regimen Comparison of Once Monthly and Once Every 4 Weeks

To bridge from the Q4W dosing regimen used in the clinical program to the once-monthly regimen proposed for commercialization, simulations were performed using the final population PK/PD model and applying the covariate distribution from Study ISIS 678354-CS3 in patients with FCS. The simulated olezarsen PK and PD profiles following the administration of olezarsen 80 mg Q4W for 13 doses or once monthly for 12 doses overlapped on Day 1 and at steady-state with only marginal difference in median (and 80% prediction interval) olezarsen concentrations and ApoC-III or TG concentrations ([Figure 3](#) and [Figure 31](#)).

The comparison of Q4W with a once-monthly dosing regimen showed no meaningful differences in the simulated PK exposure ($C_{max,ss}$, $C_{trough,ss}$, and $AUC_{tau,ss}$) ([Figure 4](#)) and ApoC-III or TG profiles when compared for different dose levels (30, 50, 80, and 120 mg) ([Figure 5](#)).

Overall, there do not appear to be any clinically relevant differences in PK, ApoC-III, or TG between the dosing regimen of Q4W and Q1M.

Figure 3. Simulated Percent Change From Baseline in ApoC-III and TG Over Time (80 mg Q4W/Q1M Dosing Regimen)

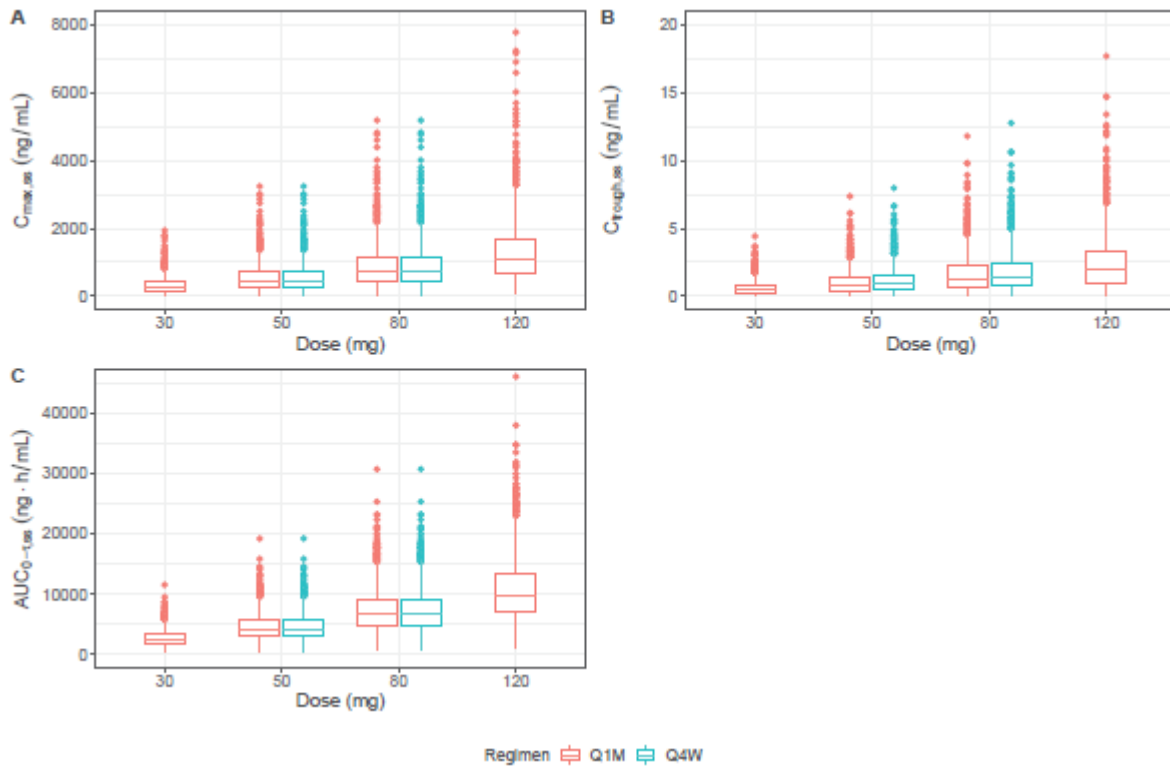


Source: FDA reviewer

Note: Solid lines: median of the simulated observations. Shaded areas: 95% CI of the simulated median observations obtained from Monte-Carlo simulations (1000 replicates of a virtual FCS population with the same demographic characteristics as study ISIS 678354-CS3 (n=43)).

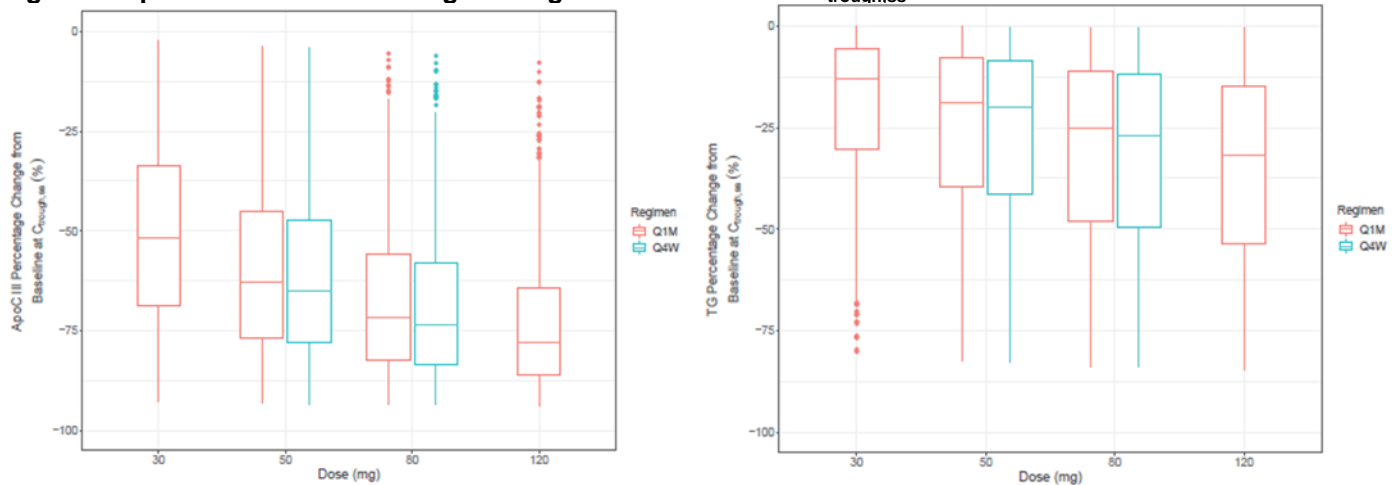
Abbreviations: CI, confidence interval; Apo, apolipoprotein; FCS, familial chylomicronemia syndrome; Q4W, every four weeks; Q1M, every 30 days; TG, triglycerides; SC, subcutaneous

Figure 4. Simulated PK Metrics at Steady-State by Dose and Dosing Regimen



Source: Figure 82 of 678354-ppk02-study-report
Abbreviations: AUC, area under the concentration-time curve; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration; PK, pharmacokinetics; Q1M, every 30 days; Q4W, every four weeks

Figure 5. ApoC-III and TG Percentage Change From Baseline at $C_{trough,ss}$



Source: Figures 83 and 84 of 678354-ppk02-study-report
Abbreviations: Apo, apolipoprotein; $C_{trough,ss}$, trough plasma concentration at steady state; TG, triglycerides; Q1M, every 30 days; Q4W, every four weeks

Bridging Between Phase 3 and To-Be-Marketed Drug Product Presentations

The bioequivalence (BE) Trial ISIS 678354-CS20, in conjunction with the exposure-response analyses for efficacy and safety, support that intended commercial 80 mg olezarsen administered

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as a 100 mg/mL formulation via autoinjector was therapeutically equivalent to 80 mg olezarsen administered as a 100 mg/mL formulation via vial with syringe, as used in the clinical program.

Table 6. Analysis of Relative Bioavailability and Bioequivalence of Plasma Olezarsen PK Parameters – Olezarsen 80 mg, Trial CS20

PK Parameter	Unit	Olezarsen 80 mg Autoinjector (Treatment C)		Olezarsen 80 mg Vial (Treatment D)		Geo Mean Ratio (Treatment C / Treatment D) (%)	90% CI for Ratio (%)
		N	Geo Mean	N	Geo Mean		
AUC _{0-336h}	h*ng/mL	47	5739	47	5061	113.4	(107.89, 119.17)
C _{max}	ng/mL	47	762	47	642	118.7	(108.86, 129.42)

Source: Reviewer's Analysis

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; Geo, geometric; PK, pharmacokinetic

The primary endpoint of BE between the autoinjector and the vial presentations based on AUC_{0-336h} was achieved but the geometric mean ratio 90% CI for C_{max} was slightly above the standard upper CI limit for BE (80.00% to 125.00%), by 4.42% (Table 6). However, this small difference is not clinically relevant based on the following considerations: (1) the short duration around C_{max}, during which plasma concentration versus time profiles showed a small difference, and the rest of the concentration-time profiles were nearly superimposable; (2) the percent changes in ApoC-III and TG levels from baseline on any of the sampling days were similar between the two treatments (autoinjector and vial). These data demonstrate that the small difference in C_{max} at the 80 mg dose level between the two treatments had no clinically meaningful effect on PD; and (3) there was no clinical meaningful difference in safety profiles and ISRs between the two presentations for olezarsen. Of note, as detailed in Section 17, the autoinjector was introduced into the open-label clinical trials, CS7 and CS13, and the exposure to the autoinjector in these trials was small.

OSIS has determined that an inspection is not needed for bioanalytical site because they conducted a Remote Regulatory Assessment for this site in (b) (4) under a different NDA and concluded that data from the reviewed studies were reliable.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Integrated Analysis, Efficacy

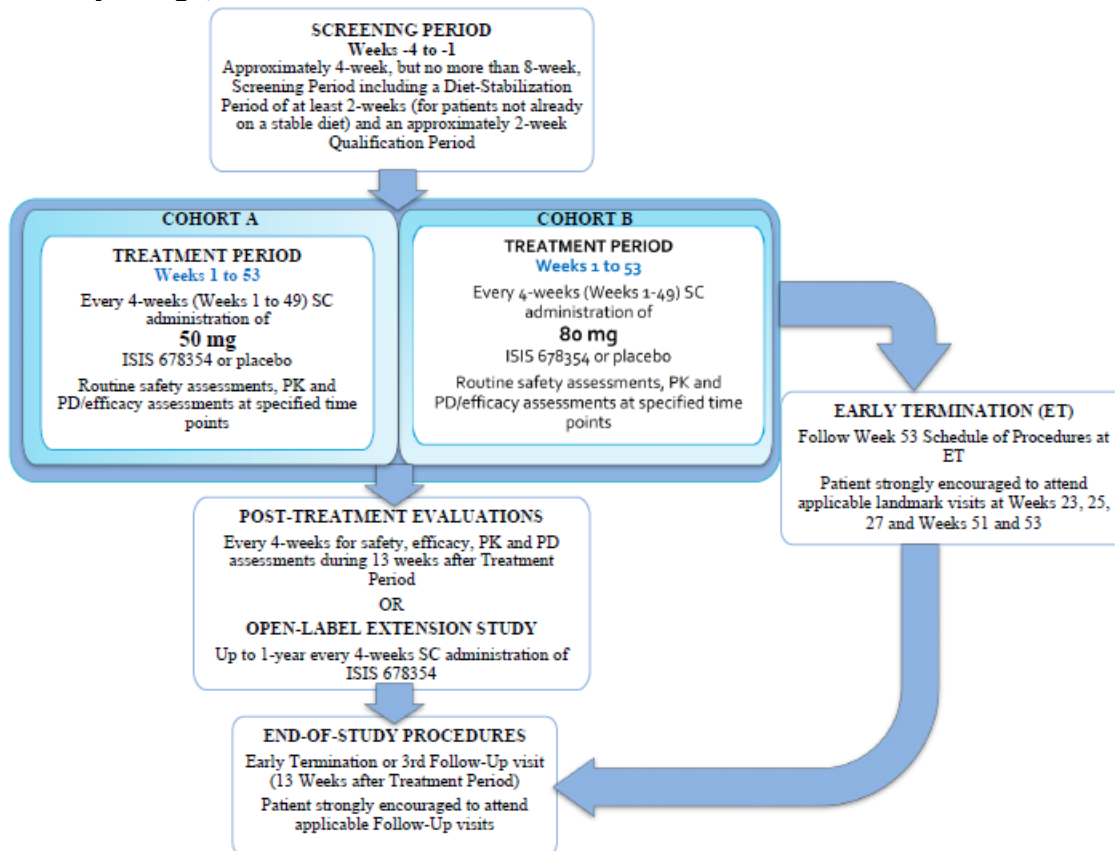
The review team concluded that an integrated analysis of efficacy was not informative given the FCS population investigated in Trial CS3 and the sHTG and moderate HTG population with increased risk/or established CVD investigated in Trial CS8 were too different in terms of baseline levels of TG and risk of pancreatitis to make comparative analyses.

6.2.2. Trial ISIS 678354-CS3

6.2.2.1. Design, Trial CS3

The pivotal Trial ISIS 678354-CS3 (Trial CS3) was a randomized, double blind, placebo-controlled trial in patients with FCS with and without a prior history of pancreatitis. The primary objective of this trial was to demonstrate the efficacy of olezarsen (two different doses) on the percent change in fasting TG over a 53-week period compared to placebo. Subjects were randomized in a 1:1 ratio to either cohort A (50 mg) or Cohort B (80 mg). Each cohort was further randomized 2:1 to receive olezarsen or placebo. Randomization was stratified by prior history of pancreatitis (within 10 years prior to screening) and previous treatment with volanesorsen. The study design is shown below (Figure 6).

Figure 6. Study Design, Trial CS3



Abbreviations: ET = Early Termination; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous.

Source: Complete Study Report, Trial CS3.

The primary efficacy endpoint was change in fasting TG from baseline to Month 6 (defined as the average of Weeks 23, 25, and 27). The primary endpoint family included analysis of the percent change in fasting TG from baseline at Month 6 first for the olezarsen 80 mg group, and, if the comparison with placebo was statistically significant for the olezarsen 80 mg group, then

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Tryngolza (olezarsen sodium)

superiority over placebo of the percent change in fasting TG from baseline at Month 6 for the olezarsen 50 mg group was to be determined.

The effect on AP events was also evaluated in this trial. Out of a total of 28 secondary endpoints, a comparison of adjudicated AP between the olezarsen treatment arms and placebo was listed in endpoints #13-16, and #25-26 (see below).

Other FCS-related symptoms were assessed as exploratory endpoints.

Primary Endpoint

- Percent change in fasting TG from baseline at Month 6 (average of Weeks 23, 25, and 27) for olezarsen 80 mg compared to placebo*
- Percent change in fasting TG from baseline at Month 6 (average of Weeks 23, 25, and 27) for olezarsen 50 mg compared to placebo

** If the primary endpoint for olezarsen 80 mg was significant, then the analysis for olezarsen 50 mg was to be determined*

Key Secondary Endpoints

The following list highlights key secondary endpoints; refer to Section [III](#) for the complete list.

- Secondary endpoint 1: comparison of percent change in fasting TG from baseline to Month 12 (Month 12 for all assessments is an average of Weeks 51 and 53) between olezarsen 80 mg group and pooled placebo in full analysis set (FAS)
- Secondary endpoint 2: comparison of percent change in fasting ApoC-III from baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 3: comparison of percent change in fasting ApoC-III from baseline to Month 12 between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 4: comparison of proportion of patients who achieve $\geq 40\%$ reduction in fasting TG from baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 5: comparison of percent change in fasting ApoB-48 from baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 6: comparison of percent change in fasting non-HDL-C from baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 7: comparison of percent change in fasting TG from baseline to Month 12 between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 8: comparison of percent change in fasting ApoC-III from baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 9: comparison of percent change in fasting ApoC-III from baseline to Month 12 between olezarsen 50 mg group and pooled placebo in FAS

- Secondary endpoint 10: comparison of proportion of patients who achieve $\geq 40\%$ reduction in fasting TG from baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 11: comparison of percent change in fasting ApoB-48 from baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 12: comparison of percent change in fasting non-HDL-C from baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 13: comparison of adjudicated AP event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening
- Secondary endpoint 14: comparison of adjudicated AP event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in FAS
- Secondary endpoint 15: comparison of adjudicated AP event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening
- Secondary endpoint 16: comparison of adjudicated AP event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the FAS
- Secondary endpoint 17: comparison of proportion of patients who achieve $\geq 70\%$ reduction in fasting TG from baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 18: comparison of percent change in fasting non-HDL-C from baseline to Month 12 between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 19: comparison of percent change in fasting ApoB-48 from baseline to Month 12 between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 20: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between olezarsen 80 mg group and pooled placebo in the FAS
- Secondary endpoint 21: comparison of proportion of patients who achieve $\geq 70\%$ reduction in fasting TG from baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 22: comparison of percent change in fasting non-HDL-C from baseline to Month 12 between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 23: comparison of percent change in fasting ApoB-48 from baseline to Month 12 between olezarsen 50 mg group and pooled placebo in FAS
- Secondary endpoint 24: comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point between olezarsen 50 mg group and pooled placebo in the FAS

- Secondary endpoint 25: comparison of adjudicated AP event rate from Week 1 to 53 between pooled olezarsen treatment group and pooled placebo in the subset of FAS with two or more events of adjudicated AP in 5 years prior to enrollment
- Secondary endpoint 26: comparison of adjudicated AP event rate from Week 13 to 53 between pooled olezarsen treatment group and pooled placebo in the subset of FAS with two or more events of adjudicated AP in 5 years prior to enrollment
- Secondary endpoint 27: comparison of proportion of patients who achieve fasting TG $\leq$ 500 mg/dL at the primary analysis time point between olezarsen 80 mg group and pooled placebo in FAS
- Secondary endpoint 28: comparison of proportion of patients who achieve fasting TG $\leq$ 500 mg/dL at the primary analysis time point between olezarsen 50 mg group and pooled placebo in FAS

Exploratory Endpoints

- Patient-reported abdominal pain, other FCS-related symptoms (physical fatigue, difficulty thinking, and diarrhea), diet, and impacts, health-related quality of life (HRQoL), pain interference, and cognitive function. Refer to Section [16.3](#) for a more detailed description of the clinical outcome assessment instrument and results.
- Emergency room (ER) visits, incidence of all-cause hospitalizations and total inpatient days

6.2.2.2. Eligibility Criteria, Trial CS3

Main Inclusion Criteria

1. A diagnosis of FCS (type 1 hyperlipoproteinemia) by documentation of confirmed homozygote, compound heterozygote, or double heterozygote for loss-of-function mutations in type 1-causing genes, such as LPL, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), apolipoprotein A5 (ApoA5), apolipoprotein C-II (ApoC2), glycerol-3 phosphate dehydrogenase 1 (GPD1), or lipase maturation factor 1 (LMF1).
2. Fasting TG $\geq$ 880 mg/dL at screening. If the fasting TG was $<$ 880 mg/dL, up to two additional tests may have been performed, with any single test used to qualify
3. Age $\geq$ 18 years at the time of informed consent
4. History of pancreatitis (defined as a recorded diagnosis of AP or hospitalization or ER visit for severe abdominal pain consistent with AP and for which no alternate diagnosis was made) within 10 years prior to screening. Patients without a recorded history of pancreatitis,

or no recorded history within 10 years prior to screening, were also eligible but their enrollment was capped at 35% (i.e., ≤ 21) of the 60 planned patients.

5. Willing to follow a diet comprising ≤ 20 g of fat per day during the study
6. The following concomitant medications were allowed if on a stable dose for at least 4 weeks prior to screening:

Statins, omega-3 fatty acids, prescription and over-the-counter (OTC), fibrates, or other lipid-lowering medications

Antidiabetic medications

Antihypertensive medications

Oral anticoagulants

Tamoxifen, estrogens or progestins

Main Exclusion Criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening) or physical examination
2. AP within 4 weeks prior to screening
3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would have rendered a patient unsuitable for inclusion:

Platelet count $< 100,000/\text{mm}^3$ at Screening or Qualification. If the platelet count was $< 100,000/\text{mm}^3$, up to two additional tests may have been performed to qualify at both screening and qualification

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3.0 \times$ upper limit of normal (ULN)

Total bilirubin $> \text{ULN}$ unless due to Gilbert's syndrome

Estimated glomerular filtration rate (eGFR) $< 45 \text{ mL/min/1.73 m}^2$ (as determined by the Chronic Kidney Disease Epidemiology formula for creatinine clearance)

Urine protein/creatinine ratio (UPCR) $\geq 500 \text{ mg/g}$, or urine albumin/creatinine (UACR) ratio $\geq 300 \text{ mg/g}$

4. Uncontrolled arterial hypertension (blood pressure [BP] $> 160/100 \text{ mm Hg}$)
5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at screening
6. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that had been successfully treated
7. Active infection with HIV, hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C.
8. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 1 month of screening, or five half-lives of investigational agent, whichever was longer

The above eligibility criteria are acceptable.

6.2.2.3. Patient Screening and Disposition, Trial CS3

A total of 144 subjects were screened for the trial. Of those screened, approximately 54% failed screening due mostly to failure to meet randomization criteria (69), other (6), physician decision (2), and withdrawal by patient (1). The reason “Other” for screen failure was further investigated (Listing 16.2.1.2). In most cases (5 out of 6) it was due to subject not able to meet according to visit schedule.

Table 7. Subject Screening and Enrollment, Trial CS3

Disposition	Trial ISIS-678354-CS3
Patients screened	144
Screening failures	78
Failure to meet randomization criteria	69
Other	6
Physician decision	2
Withdrawal by subject	1
Patients randomized	66

Source: Clinical Analyst; ds.xpt and Clinical Study Report; Software: R

A total of 66 subjects were randomized to receive olezarsen (olezarsen 80 mg, n=22; olezarsen 50 mg, n=21) or placebo (n=23). The number of patients in each treatment group with prior history of pancreatitis within 10 years of Screening and with previous treatment with volanesorsen were similar, due to stratified randomization.

Approximately 88% or 38/43 subjects in the pooled olezarsen treatment group completed the study. [Table 8](#) below summarizes the disposition of subjects by treatment arm.

Overall, five subjects (5/43 or 11.6%) discontinued pooled olezarsen treatment (three subjects in the olezarsen 80 mg group, two subjects in the olezarsen 50 mg group) compared to one subject in the placebo group.

Overall, three subjects (3/43 or 7.0%) in the pooled olezarsen group discontinued study drug due to an adverse event (AE); no patients in the placebo group discontinued treatment due to an AE. One of the discontinuations due to an AE was a sudden death in the olezarsen 50 mg group which is further examined in the safety review.

Across the treatment groups, the percentage of subjects that completed the trial was balanced and allowed for a meaningful assessment of efficacy and safety.

Table 8. Subject Disposition, Trial CS3

Disposition Outcome	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=21 n (%)	N=22 n (%)	N=23 n (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
Patients randomized	21	22	23	NA	NA
Per-protocol population	18	19	22	NA	NA
Safety population	21	22	23	NA	NA
Study treatment termination	21 (100)	22 (100)	23 (100)	0.0 (-15.8, 14.6)	0.0 (-15.2, 14.6)
Completed	19 (90.5)	19 (86.4)	22 (95.7)	-5.2 (-25.6, 13.3)	-9.3 (-30.1, 9.7)

Disposition Outcome	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg N=21 n (%)	80 mg N=22 n (%)		50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Discontinued study drug	2 (9.5)	3 (13.6)	1 (4.3)	5.2 (-13.3, 25.6)	9.3 (-9.7, 30.1)
Adverse event	1 (4.8)	2 (9.1)	0	4.8 (-10.2, 23.0)	9.1 (-6.2, 28.1)
Physician decision	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Withdrawal by subject	1 (4.8)	1 (4.5)	0	4.8 (-10.2, 23.0)	4.5 (-10.4, 22.1)

Source: ds.xpt and adsl.xpt; Software: R

Duration is up to 400 days. Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; n, number of patients in specified population or group; N, number of patients in treatment arm; NA, not applicable

6.2.2.4. Patient Demographics, Trial CS3

[Table 9](#) provides the demographics and baseline characteristics for the subjects enrolled in Trial CS3. There are no significant differences in these baseline characteristics between treatment or placebo arms.

Table 9. Baseline Demographics and Clinical Characteristics, Trial CS3

Characteristic	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Placebo N=23
Sex, n (%)			
F	15 (71.4)	11 (50.0)	12 (52.2)
M	6 (28.6)	11 (50.0)	11 (47.8)
Age, years			
Mean (SD)	43.2 (12.1)	47.7 (13.3)	44.0 (14.7)
Median (min, max)	42 (18, 74)	47 (25, 78)	46 (21, 69)
<40 years	6 (28.6)	7 (31.8)	9 (39.1)
≥40 to <65 years	14 (66.7)	13 (59.1)	11 (47.8)
≥65 years	1 (4.8)	2 (9.1)	3 (13.0)
Baseline BMI group, n (%)			
<18.5 BMI	4 (19.0)	1 (4.5)	3 (13.0)
≥18.5 to ≤25 BMI	13 (61.9)	13 (59.1)	9 (39.1)
>25 to ≤30 BMI	3 (14.3)	6 (27.3)	10 (43.5)
>30 BMI	1 (4.8)	2 (9.1)	1 (4.3)
Baseline weight (kg) group, n (%)			
<50 kg	2 (9.5)	2 (9.1)	4 (17.4)
≥50 to <65 kg	13 (61.9)	7 (31.8)	8 (34.8)
≥65 kg	6 (28.6)	13 (59.1)	11 (47.8)
Diabetic status, n (%)			
No	18 (85.7)	15 (68.2)	17 (73.9)
Yes	3 (14.3)	7 (31.8)	6 (26.1)
Pancreatitis history, n (%)			
No	6 (28.6)	5 (22.7)	8 (34.8)
Yes	15 (71.4)	17 (77.3)	15 (65.2)
Genetic confirmation of FCS, n (%)			
Yes	21 (100)	22 (100)	23 (100)

Characteristic	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Placebo N=23
LPL gene status, n (%)			
Compound heterozygous	3 (14.3)	5 (22.7)	5 (21.7)
Double heterozygous	0	1 (4.5)	0
Hemizygous	0	1 (4.5)	0
Homozygous	14 (66.7)	10 (45.5)	16 (69.6)
Missing	4 (19.0)	5 (22.7)	2 (8.7)
Race, n (%)			
Asian	3 (14.3)	3 (13.6)	0
Native Hawaiian or Other Pacific Islander	1 (4.8)	0	0
Other	0	2 (9.1)	1 (4.3)
White	17 (81.0)	17 (77.3)	22 (95.7)
Ethnicity, n (%)			
Hispanic or Latino	3 (14.3)	1 (4.5)	3 (13.0)
Not Hispanic or Latino	18 (85.7)	21 (95.5)	20 (87.0)
Country of participation, n (%)			
Canada	4 (19.0)	1 (4.5)	5 (21.7)
Spain	5 (23.8)	2 (9.1)	3 (13.0)
Italy	0	3 (13.6)	3 (13.0)
Netherlands	3 (14.3)	2 (9.1)	1 (4.3)
United States	5 (23.8)	7 (31.8)	7 (30.4)
Others	4 (19)	7 (31.8)	4 (17.4)
Is in U.S., n (%)			
U.S.	5 (23.8)	7 (31.8)	7 (30.4)
Non-U.S.	16 (76.2)	15 (68.2)	16 (69.6)

Source: Clinical Analyst

Abbreviations: BMI, body mass index; F, female; FCS, familial chylomicronemia syndrome; LPL, lipoprotein lipase; M, male

[Table 10](#) summarizes the baseline lipid and lipoprotein levels for Trial CS3.

Table 10. Summary of Baseline Triglycerides, Other Lipids, and Lipoproteins, Trial CS3

Baseline Characteristics/ Statistic	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Placebo N=23
Fasting triglycerides (mg/dL)			
Mean (SD)	2683.8 (1235.1)	2613.1 (1499.0)	2595.7 (1255.7)
Median (minimum, maximum)	2678.5 (779, 5965)	2086.0 (682, 6898)	2493.0 (334, 5436)
Fasting apoC-III (mg/dL)			
Mean (SD)	27.7 (10.5)	27.5 (11.6)	27.7 (11.7)
Median (minimum, maximum)	27.8 (11, 51)	28.4 (10, 49)	25.6 (9, 55)
Fasting total cholesterol (mg/dL)			
Mean (SD)	323.4 (100.5)	277.4 (99.3)	286.0 (113.9)
Median (minimum, maximum)	341.0 (185, 470)	263.8 (94, 545)	266.0 (46, 508)
Fasting LDL-C - ultracentrifugation (mg/dL)			
Mean (SD)	17.6 (8.5)	22.8 (14.1)	16.7 (8.4)
Median (minimum, maximum)	16.0 (7, 46)	21.0 (3, 56)	13.0 (4, 38)
Fasting HDL-C (mg/dL)			
Mean (SD)	15.7 (4.0)	14.5 (4.5)	14.7 (3.8)
Median (minimum, maximum)	16.0 (8, 24)	15.3 (5, 23)	14.5 (8, 27)

Baseline Characteristics/ Statistic	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Placebo N=23
Fasting apoB (mg/dL)			
Mean (SD)	65.2 (13.5)	58.4 (17.2)	59.8 (19.0)
Median (minimum, maximum)	65.2 (34, 97)	58.0 (32, 85)	53.0 (33, 117)
Fasting apoB-48 (mg/dL)			
Mean (SD)	18.6 (15.3)	11.7 (8.1)	14.2 (14.2)
Median (minimum, maximum)	12.8 (4, 60)	8.8 (2, 29)	8.4 (1, 61)
Fasting chylomicron-TG (mg/dL)			
Mean (SD)	2302.3 (1265.3)	2477.0 (2123.4)	2268.7 (1237.0)
Median (minimum, maximum)	2066.5 (449, 5696)	1875.5 (375, 9867)	1958.0 (227, 4852)
Fasting chylomicron-C + VLDL-C (mg/dL)			
Mean (SD)	293.2 (103.3)	245.7 (110.9)	255.4 (114.4)
Median (minimum, maximum)	314 (122, 451)	222.8 (63, 572)	244 (30, 490)
Fasting non-HDL-C (mg/dL)			
Mean (SD)	307.4 (101.8)	262.9 (100.4)	271.3 (113.3)
Median (minimum, maximum)	327.0 (167, 458)	247.0 (77, 540)	251.0 (38, 494)

Source: Clinical Study Report Study Number ISIS 678354-CS3, Table 10, pages 86-87

Abbreviations: Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol

Baseline lipid and lipoprotein levels were generally consistent across treatment arms. Mean fasting TG levels at baseline were 2613.1, 2683.8, and 2595.7 mg/dL for the olezarsen 80 mg group, olezarsen 50 mg group, and placebo group, respectively. Mean fasting ApoC-III levels at baseline were 27.54 mg/dL, 27.73 mg/dL, and 27.68 mg/dL for the olezarsen 80 mg, olezarsen 50 mg, and placebo treatment groups, respectively.

6.2.2.5. Statistical Analysis Plan, Trial CS3

Analysis Population

The FAS was defined as all patients who were randomly assigned to treatment and received any amount of olezarsen or placebo. The primary efficacy analysis was performed using FAS. The safety set was also defined as all patients who were randomized to treatment and received any amount of olezarsen or placebo. The safety analysis was performed using the safety set.

Primary Efficacy Analysis

The primary analysis time point was at Month 6. The value of the primary endpoint was defined as the average of Week 23, 25, and 27 fasting assessments. The Applicant's prespecified primary analysis of the primary endpoint, the mean percent change in fasting TG from baseline to the primary analysis time point, was performed using an analysis of covariance (ANCOVA) model with missing values imputed using the retrieved dropout method (patients who discontinue treatment before Week 23 but still have TG assessments at Weeks 23, 25, or 27). The model included treatment group (olezarsen 80 mg, olezarsen 50 mg, pooled placebo) and the two randomization stratification factors (prior history of pancreatitis within 10 years prior to screening (yes vs. no) and previous treatment with volanesorsen (yes vs. no) as the fixed effects and natural log-transformed baseline fasting TG as a covariate. To account for potential heterogeneity in variance, the 95% CIs were calculated using the robust variance estimator based on the Bell and McCaffrey method. The Applicant stated that any intercurrent events occurring

before Week 23 (e.g., treatment discontinuation, use of additional medication, changes in background or concomitant treatments) were implemented using the treatment policy strategy where the patients' assessments post intercurrent events were collected and used in the analysis. The Applicant conducted a post hoc test for normality based on the observed data using a Shapiro-Wilk Normality Test. The FDA results shown are different from the Applicant's results, but the conclusions concur.

Missing Data

There was about 7.5% missing data at Month 6 (one patient in olezarsen 50 mg, three patients in olezarsen 80 mg, and one patient in the placebo group). There was not a sufficient number of retrieved dropouts, thus the Applicant used a washout multiple imputation approach (Jump to Reference, J2R) to impute missing TG data. The Applicant stated that patients treated with olezarsen who had missing TG values after the last dosing date multiply imputed based on baseline fasting TG, the two stratification factors of their own treatment group, and the imputation model for the placebo group. Patients in the placebo group had missing TG values multiply imputed based on baseline fasting TG, fasting TG values at postbaseline visits and the two stratification factors from the placebo group.

There was some concern over how the missing data were imputed. We were unable to replicate the results. An information request was sent to the Applicant seeking clarification on whether their imputation procedure had taken into account all uncertainties of the estimated imputation model based on placebo data. It seems that the Applicant selected the first 100 imputed datasets with the imputed values falling into feasible range of the imputed endpoints among 500 imputations. This procedure may underestimate the uncertainty of the imputed values. In response to the information request, the Applicant performed alternative imputation by directly restricting the imputed values to be within the feasible range instead of discarding out of range imputations. FDA conducted a washout imputation in the primary analysis to impute missing data without truncating any imputed values. FDA results are shown in Section [6.2.2.6](#). The results are different from the Applicants, but the conclusion remained the same. FDA's analyses used only placebo completer data for the placebo-washout imputation whereas the Applicant's imputation used all observed placebo data, which also contributed to the difference in results.

The Applicant conducted some sensitivity analyses in the FAS population to evaluate the impact of missing data on the analysis conclusion for the primary endpoint. A pattern mixture model with ANCOVA was conducted, as well as a nonparametric analysis with Wilcoxon rank-sum test, a two-dimensional tipping-point analysis, and an ANCOVA model using log-transformed data. The results of the nonparametric analysis with Wilcoxon rank-sum will be shown in this review.

Secondary Endpoints

There are many secondary endpoints (see Section 6.2.2.1 and Section III). This review will present results of (b) (4).

- Percent change in fasting TG from baseline at Month 12
- Percent change in fasting ApoC-III from baseline at Month 6 and Month 12
- Percent change in fasting ApoB-48 from baseline at Month 6 and Month 12
- Percent change in fasting non-HDL-C from baseline at Month 6 and Month 12
- Adjudicated AP event rate.

(b) (4)

- Adjudicated AP event rate in patients with a prior history of pancreatitis within 10 years prior to screening
- Adjudicated AP event rate between pooled olezarsen and pooled placebo in the subset of patients with two or more adjudicated AP events in 5 years prior to enrollment (FAS).

There are some endpoints of interest to the FDA that were not included in the main clinical study report by the Applicant that are also shown in this review:

- Percent change in baseline in LDL-C ultracentrifugation (mg/dL)
- Percent change in baseline in fasting total ApoB (mg/dL)
- Percent change in baseline in fasting high density lipoprotein cholesterol (mg/dL).

Note: Month 12 value was defined as the average of Weeks 51 and 53 values of an endpoint.

The continuous secondary endpoints were analyzed similarly to the primary endpoint with the same missing data imputation implemented. FDA conducted a washout imputation to impute missing data without truncating any imputed values.

The pancreatitis endpoints were analyzed using a negative binomial regression model with treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated AP events in 5 years prior to the enrollment, i.e., events occurred within 1,826 days (calculated by 365.25 times 5 and rounded to integer) before the first dose date and up to the first dose date and time, as a covariate. The logarithm of time in year that each patient was observed from Week 1 to 53 was used as an offset variable.

Multiplicity

A step-down procedure to account for multiplicity across treatment comparisons and key endpoints was used. For the primary endpoint family, the two treatment arms (olezarsen 80 mg and olezarsen 50 mg) were compared against pooled placebo using the hierarchical testing procedure, in which the olezarsen 80 mg treatment group was first compared to the pooled placebo at the 2-sided alpha level of 0.05. If the comparison was statistically significant ($p < 0.05$), then the olezarsen 50 mg treatment group was compared against the pooled placebo at the alpha level of 0.05. If the comparison of the olezarsen 80 mg treatment group was not

statistically significant, then the comparison of the olezarsen 50 mg treatment group against pooled placebo and all secondary endpoints were considered exploratory.

Testing of the secondary endpoint family was performed only if the comparison of the primary endpoint was statistically significant ($p < 0.05$) for both the olezarsen 80 mg and 50 mg treatment groups. If the comparison of the first secondary endpoint was statistically significant ($p < 0.05$), then the second secondary endpoint was tested. However, if the comparison of the first secondary endpoint was not statistically significant, then all endpoints of lower rank were considered exploratory. This process was repeated with each subsequent secondary endpoint.

6.2.2.6. Results of Analyses, Trial CS3

The primary analysis results for the mean percent change in fasting TG from baseline at Month 6 are shown in [Table 11](#). A statistically significantly greater mean percent decrease in fasting TG levels from baseline at Month 6 was observed in the olezarsen 80 mg group compared with the placebo group; the placebo-subtracted treatment difference was -44.5%, $p = 0.0015$. Statistical significance was not achieved for the olezarsen 50 mg group compared with the pooled placebo group; the placebo-subtracted treatment difference was -21.5%, $p = 0.1153$.

Table 11. Primary Analysis: Mean Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 6, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	2683.8 (1235.1)	2613.1 (1499.0)	2595.7 (1255.7)
LS means (SD)	-10.3 (9.8)	-33.3 (10.2)	11.2 (8.9)
Treatment difference, olezarsen-placebo	-21.5	-44.5	
95% CI	-48.2, 5.3	-72.0, -17.0	
P-value	0.1153	0.0015	

Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed baseline triglyceride as a covariate.

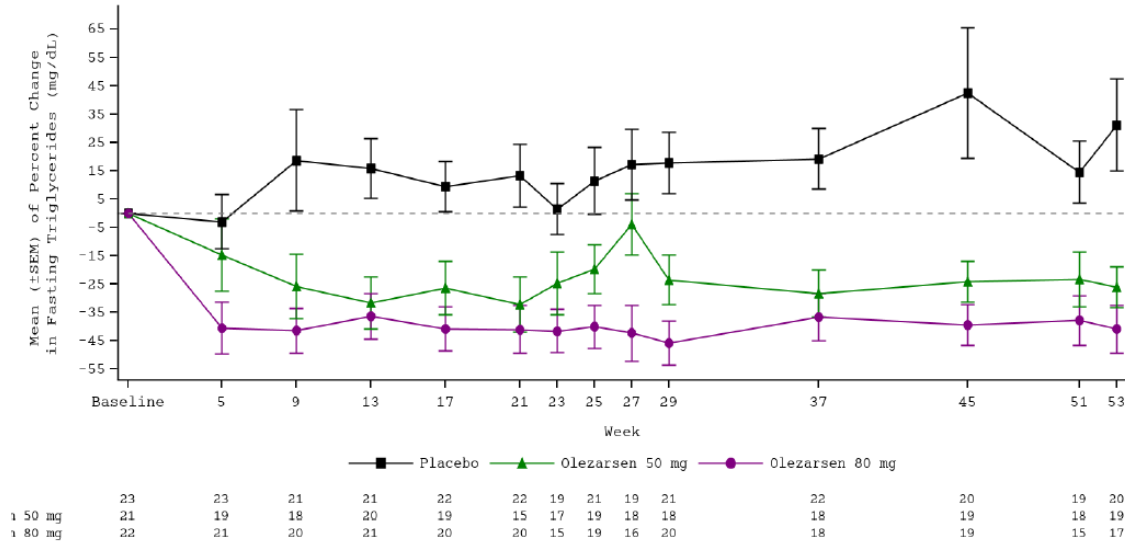
Missing data were imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Figure 7](#) displays the observed mean percent change from baseline in fasting TG over time (without a missing data imputation). Olezarsen 50 mg only failed around Week 27, where the fasting TG levels increased, then had a significant effect at other timepoints until Month 12. The reasons for this shift in the levels is unclear.

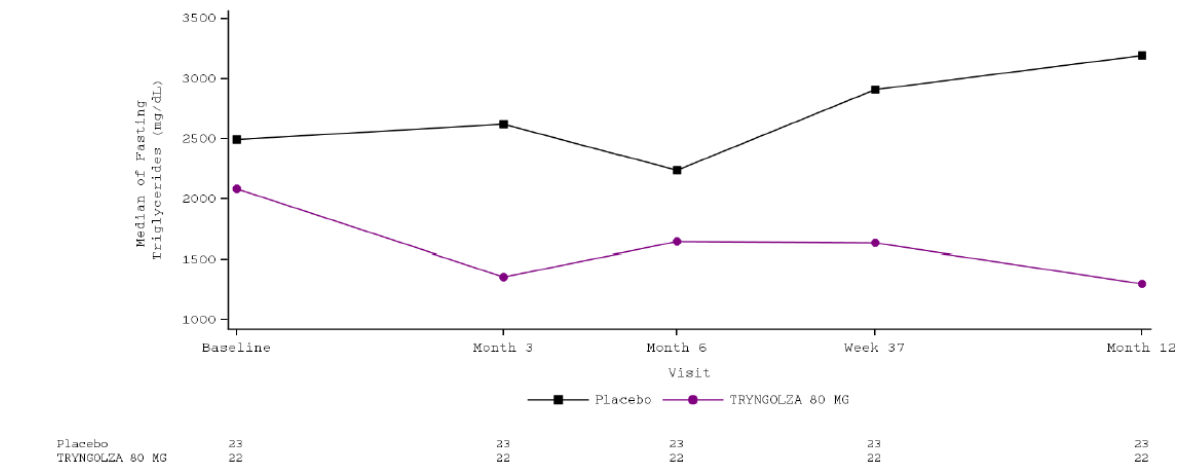
Figure 7. Mean ($\pm$ SEM) Percent Change From Baseline in Fasting Triglycerides (mg/dL) Over Time, Full Analysis Set, Trial CS3



Source: Clinical Study Report- Trial ID: ISIS 678354-CS3 Figure 4, page 101
 Abbreviations: SEM, standard error of the mean

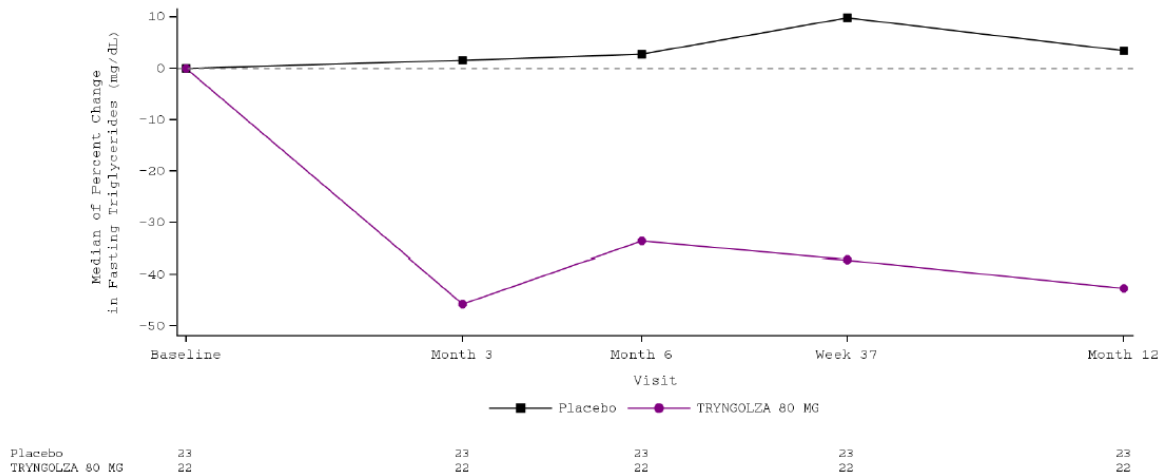
Figure 8 displays the median fasting TG (mg/dL) over time, where missing data was imputed. Figure 9 displays median percent change in fasting TG (mg/dL) over time with missing data imputed. Both figures are by treatment group (80 mg vs. placebo). The figures show a greater decrease in the olezarsen 80 mg group compared to placebo over a 12-month period.

Figure 8. Median Fasting Triglycerides (mg/dL) Over Time, Full Analysis Set, Trial CS3



Where data was missing, the median value across the imputed datasets for each patient was used in the figure.
 Source: Response to Agency Information Request Study Number ISIS 678354-CS3, Figure FDA IR 2.1a, page 6

Figure 9. Median Percent Change in Fasting Triglycerides (mg/dL) Over Time (Full Analysis Set)



Where data was missing, the median value across the imputed datasets for each patient was used in the figure.

Source: Response to Agency Information Request Study Number ISIS 678354-CS3, Figure FDA IR 2.2a, page 7

The results of the nonparametric analysis with Wilcoxon rank-sum test are shown in [Table 12](#) for the FAS population. The results were very similar to the prespecified primary analysis results for using the mean percent change, in favor of olezarsen, with the 80 mg group showing a greater median decrease compared to pooled placebo. Specifically, the placebo-subtracted treatment difference in median percent change from baseline at Month 6 was -40.8%.

Table 12. Sensitivity Analysis: Median Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 6, Non-Parametric Analysis With Wilcoxon Rank-Sum Test, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline median (P25, P75)	2678.5 (1743.5, 3168.0)	2086.0 (1778.0, 3141.0)	2493.0 (1653.0, 3605.0)
Month 6 median (P25, P75)	2106.7 (1705.9, 2528.5)	1645.3 (1053.3, 2016.1)	2239.0 (1486.0, 3715.0)
% change from baseline median (P25, P75)	-13.8 (-48.7, 18.5)	-33.6 (-54.3, -9.0)	2.8 (-21.0, 36.4)
Treatment difference, olezarsen-placebo	-21.6	-40.8	
95% CI	(-49.0, 5.9)	(-65.5, -16.1)	

Source: Response to Agency Information Request Study Number ISIS 678354-CS3, Table FDA IR 1.1a, page 4

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27.

Note: Missing data for patients in the olezarsen arms were imputed using washout MI (J2R) approach. Missing data for patients in the placebo group were imputed under the MAR assumption. Where endpoint was missing, the median value across the imputed datasets for each patient was used in the summary. For each imputed data set, Wilcoxon rank-sum test for percent change from baseline to endpoint was performed. Hodges-Lehmann estimate of the location shift with 95% CI, and Wilcoxon Rank Sum test p-value were the overall estimates combined from all 100 tests.

Abbreviations: CI, confidence interval; J2R, Jump to Reference; MAR, missing at random; MI, multiple imputation; N, total number of subjects; P25, 25th percentile; P75, 75th percentile

Because the second primary endpoint did not achieve superiority according to the pre-specified multiplicity plan, inferential statistical analysis may not proceed to the secondary efficacy

endpoints. However, they are of clinical interest and will be discussed. These endpoints are used as exploratory endpoints to support the primary endpoint.

[Table 13](#) shows the results for mean percent change in fasting TG from baseline at Month 12. Note that the results were in favor of olezarsen, with the 80 mg group showing a greater mean decrease compared to pooled placebo; the placebo-subtracted treatment difference was -61.4%.

Table 13. Secondary Endpoint: Mean Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	2683.8 (1235.1)	2613.1 (1499.0)	2595.7 (1255.7)
LS means (SD)	-21.5 (13.8)	-39.7 (14.6)	21.6 (12.7)
Treatment difference, olezarsen-placebo	-43.2	-61.4	
95% CI	-82.7, -3.6	-101.9 -20.8	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefx.xpt

Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline triglyceride as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 14](#) shows the results for fasting ApoC-III at Months 6 and 12. The results show a similar mean percent decrease in fasting ApoC-III from baseline at Months 6 and 12 for both olezarsen groups.

Table 14. Secondary Endpoint: Mean Percent Change in Baseline in Fasting ApoC-III (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	27.7 (10.5)	27.5 (11.6)	27.7 (11.7)
Month 6			
LS means (SD)	-57.0 (8.0)	-65.6 (8.6)	7.5 (7.4)
Treatment difference, olezarsen - placebo	-64.5	-73.1	
95% CI	-84.2, -44.7	-97.3, -48.8	

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Month 12			
LS means (SD)	-58.7 (11.9)	-58.7 (14.4)	17.4 (10.8)
Treatment difference, olezarsen – placebo	-76.1	-76.1	
95% CI	-104.2, -48.1	-114.6, -37.5	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefx.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: ApoC-III, apolipoprotein C-III; CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 15](#) shows the results for fasting apolipoprotein B (ApoB)-48 at Months 6 and 12. The results show a mean percent decrease in fasting ApoB-48 from baseline at Months 6 and 12 for both olezarsen groups. A greater decrease is seen in the 80 mg olezarsen group at Months 6 and 12.

Table 15. Secondary Endpoint: Mean Percent Change in Baseline in Fasting ApoB-48 (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	18.6 (15.3)	11.7 (8.1)	14.2 (14.2)
Month 6			
LS means (SD)	-5.9 (20.2)	-57.5 (19.9)	25.1 (20.2)
Treatment difference, olezarsen -placebo	-31.1	-82.7	
95% CI	-85.8, 23.7	-144.9, -20.5	
Month 12			
LS means (SD)	-32.1 (29.9)	-75.0 (28.5)	-1.0 (33.0)
Treatment difference, olezarsen -placebo	-31.1	-74.0	
95% CI	-131.9, 69.8	-174.3, 26.2	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefx.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: ApoB-48, apolipoprotein B-48; CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 16](#) shows the results for fasting non-HDL-C at Months 6 and 12. The mean percent decrease in fasting non-HDL-C levels from baseline at Months 6 and 12 for both olezarsen groups are seen. A greater decrease is seen in the 80 mg olezarsen group, with a placebo-subtracted difference of -25.7% at Month 6 and -40.6% at Month 12.

Table 16. Secondary Endpoint: Mean Percent Change in Baseline in Fasting Non-HDL-C (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	307.6 (101.8)	262.9 (100.4)	271.3 (113.3)
Month 6			
LS means (SD)	-12.2 (6.6)	-20.0 (6.8)	5.8 (5.9)
Treatment difference, olezarsen - placebo	-17.9	-25.7	
95% CI	-36.9, 1.1	-44.3, -7.1	
Month 12			
LS means (SD)	-16.8 (9.8)	-28.5 (9.9)	12.1 (8.7)
Treatment difference, olezarsen - placebo	-29.0	-40.6	
95% CI	-58.2, 0.3	-69.0, -12.2	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefl.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LS, least squares; N, total number of subjects; SD, standard deviation

The following results are the endpoints of LDL-C, total ApoB, and HDL-C that are of interest to the FDA (refer to Sections 6.3.5 and 16 for additional discussion). Table 17 shows the results for fasting LDL-C at Months 6 and 12.

Table 17. Mean Percent Change in Baseline in Fasting LDL-C Ultracentrifugation (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	17.6 (8.5)	22.8 (14.1)	16.7 (8.4)
Month 6			
LS means (SD)	33.5 (21.1)	68.3 (22.0)	11.0 (19.5)
Treatment difference, olezarsen - placebo	22.6	57.3	
95% CI	-13.4, 58.5	0.9, 113.7	
Month 12			
LS means (SD)	53.0 (15.2)	46.8 (15.8)	-0.1 (13.9)
Treatment difference, olezarsen - placebo	53.1	46.9	
95% CI	15.5, 90.7	6.4, 87.3	

Source: Statistical Reviewer's Analysis; adsl.xpt, adlb.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least squares; N, total number of subjects; SD, standard deviation

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With LDL-C, the placebo-subtracted mean treatment difference between olezarsen 80 mg and placebo was an increase of +57.3% at Month 6 at +46.9% at Month 12 ([Table 17](#)).

[Table 18](#) shows the results for fasting total ApoB at Months 6 and 12.

Table 18. Mean Percent Change in Baseline in Total ApoB (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	65.2 (13.5)	58.4 (17.2)	59.75 (19.0)
Month 6			
LS means (SD)	0.8 (8.1)	16.6 (7.9)	8.0 (7.2)
Treatment difference, olezarsen - placebo	-7.2	8.6	
95% CI	-23.0, 8.6	-14.7, 31.8	
Month 12			
LS means (SD)	1.6 (5.0)	7.8 (4.8)	0.6 (4.4)
Treatment difference, olezarsen - placebo	0.9	7.1	
95% CI	-10.8, 12.7	-5.4, 19.6	

Source: Statistical Reviewer's Analysis; adsl.xpt, adlb.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: Apo, apolipoprotein; CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 19](#) shows the results for fasting HDL-C at Months 6 and 12.

Table 19. Additional Endpoint: Mean Percent Change in Baseline in Fasting HDL-C (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Placebo N=23
Baseline mean (SD)	15.7 (4.0)	14.5 (4.5)	14.7 (3.8)
Month 6			
LS means (SD)	27.0 (7.7)	34.6 (7.7)	1.4 (7.0)
Treatment difference, olezarsen - placebo	25.6	33.3	
95% CI	8.4, 42.8	12.3, 54.2	
Month 12			
LS means (SD)	31.8 (15.7)	47.0 (15.5)	3.2 (14.2)
Treatment difference, olezarsen - placebo	28.7	43.8	
95% CI	-1.2, 58.5	-3.3, 91.0	

Source: Statistical Reviewer's Analysis; adsl.xpt, adlb.xpt

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate.

Missing data was imputed using Washout imputation.

The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LS, least squares; N, total number of subjects; SD, standard deviation

Acute Pancreatitis

In Study CS3, an independent blinded committee prospectively adjudicated all AEs suggestive of AP for which the subject visited the emergency room or was hospitalized. Of note, the committee also adjudicated retrospective AP events which occurred within 5 years of randomization using the same definitions; see Section [III](#) for more discussion of retrospective AP adjudication.

To prospectively adjudicate AP, the committee used the revised Atlanta Diagnostic Criteria ([Banks et al. 2013](#)) which required two of the following for the diagnosis of documented AP:

- Abdominal pain consistent with AP
- Serum amylase or lipase levels that were at least 3x ULN
- Computed tomography (CT)/magnetic resonance imaging findings consistent with AP

However, since clinicians do not always obtain a complete workup for AP, and to ensure that AP events were not missed, the committee defined additional categories for the diagnosis of AP:

- Probable pancreatitis- required all of the following: abdominal pain consistent with AP; typical supportive treatment for pancreatitis (such as the patient being NPO, receiving intravenous [IV] fluids, and on analgesics); amylase and lipase had to be elevated but did not have to be above 3x ULN; radiology investigations were not performed or not diagnostic; discharge diagnosis was AP with no alternative diagnosis.
- Possible pancreatitis- required all of the following: a previous medical diagnosis of AP; abdominal pain strongly consistent with AP; use of typical supportive measures for AP; serum amylase/lipase were normal or not determined or missing; radiology investigations were not performed or not diagnostic; discharge diagnosis was AP with no alternative diagnosis.
- Unable to adjudicate- insufficient source documentation.
- No diagnosis of AP- sufficient evidence provided to conclude there was no diagnosis of AP.

For data analysis, events that were decided as documented, probable, or possible were considered to be positively adjudicated AP.

The adjudication workflow for AP was such that a triggering event was randomly assigned to two adjudicators to be adjudicated independently; if there was consensus between the reviewers, the decision was complete. If there was disagreement, or if additional information was required, the event was assigned to a meeting for final adjudication. At the meeting of three reviewers, the chair would render the final decision.

In Study CS3, there were 31 prospective events adjudicated by the committee. Of the 31 events, 13 were determined to be confirmed AP events. Of the 13 events, 2 occurred in the olezarsen treatment arms (one each in the olezarsen 80 mg group and 50 mg group) and 11 events occurred in the placebo arm; the mean rate ratio (pooled olezarsen groups vs. placebo) was 0.12 (95% CI, 0.02 to 0.66, nominal p-value 0.0144) ([Table 20](#)). All subjects who had a positively confirmed AP event had a history of two or more previous episodes before the trial.

Table 20. Positively Adjudicated Acute Pancreatitis Event Rate, All Subjects, Full Analysis Set, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Olezarsen N=43	Pooled Placebo N=23
Week 1 to Week 53				
Patients with events, n (%)	1 (4.8)	1 (4.5)	2 (4.7)	7 (30.4)
Number of events	1	1	2	11
Total patient years	19.9	20.3	22.9	40.2
Mean event rate/100 patient years (95% CI)			4.4 (0.9, 20.3)	36.3 (14.7, 89.7)
Mean rate ratio: olezarsen/placebo			0.12 (0.02, 0.66)	
Week 13 to Week 53				
Patients with events, n (%)	1 (4.8)	1 (4.5)	2 (4.7)	6 (26.1)
Number of events	1	1	2	8
Total patient years	15.9	16.2	32.1	17.6
Mean event rate/100 patient years (95% CI)			5.42 (1.23, 23.90)	33.43 (13.25, 84.32)
Mean rate ratio: olezarsen/placebo			0.16 (0.03, 0.85)	

Source: Statistical Reviewer's Analysis; adsl.xpt, adadj.xpt; t678354cs3_14_2_2_5_2_premodel.xpt; t678354cs3_14_2_2_6_2_premodel.xpt

Note: The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.

Abbreviations: CI, confidence interval; N, total number of subjects

The Applicant prespecified a number of secondary efficacy analyses related to adjudicated AP. All the endpoints were of nominal significance. Note that the treatment period was “Week 1 to Week 53”. The Applicant created a second interval “Week 13-Week 53” to reflect the near steady-state (at approximately three half-lives) of olezarsen. The “Week 13-Week 53” interval is considered exploratory by the FDA.

[Table 21](#) displays the results for the adjudicated AP event rates between pooled olezarsen and pooled placebo in the subset FAS population with a prior history of pancreatitis within 10 years prior to screening for Week 1 to 53 and Week 13 to 53. There were two events that occurred in the pooled olezarsen group and 11 events in the pooled placebo group from Week 1 to 53. There was a 90% decrease in the AP event rate for the pooled olezarsen group compared to the pooled placebo group from Week 1 to 53, the estimated reference range (RR) was 0.10 with 95% CI (0.02, 0.51).

Table 21. Secondary Endpoint: Adjudicated Acute Pancreatitis Event Rate Between Pooled Olezarsen and Pooled Placebo, Subset With a Prior History of Pancreatitis Within 10 Years Prior to Screening, Full Analysis Set

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Olezarsen N=43	Pooled Placebo N=23
Patients with a prior history of pancreatitis within 10 years prior to screening	15	16	31	15

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Olezarsen N=43	Pooled Placebo N=23
Week 1 to Week 53				
Patients with events, n (%)	1 (6.7)	1 (6.3)	2 (6.5)	7 (46.7)
Number of events	1	1	2	11
Total patient years	13.7	15.6	14.8	29.3
Mean event rate/100 patient years (95% CI)			6.87 (1.64, 28.74)	66.62 (30.81, 144.06)
Mean rate ratio: olezarsen/placebo			0.10 (0.02, 0.51)	
Week 13 to Week 53				
Patients with events, n (%)	1 (6.7)	1 (6.3)	2 (6.5)	6 (40.0)
Number of events	1	1	2	8
Total patient years	11.2	11.9	23.1	11.3
Mean event rate/100 patient years (95% CI)			8.30 (1.98, 34.75)	58.29 (24.75, 137.29)
Mean rate ratio: olezarsen/placebo			0.14 (0.03, 0.71)	

Source: Statistical Reviewer's Analysis; adsl.xpt, adadj.xpt; t678354cs3_14_2_2_5_2_premodel.xpt;

t678354cs3_14_2_2_6_2_premodel.xpt

Note: The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.

Abbreviations: CI, confidence interval; N, total number of subjects

[Table 22](#) displays the results for the adjudicated AP event rates between pooled olezarsen and pooled placebo in the subset FAS population with at least two adjudicated AP events in 5 years prior to enrollment for Week 1 to 53 and Week 13 to 53. There were two events that occurred in the pooled olezarsen group and 10 events in the pooled placebo group from Week 1 to 53. There was an 86% decrease in the adjudicated AP event rate for the pooled olezarsen group compared to the pooled placebo group from Week 1 to 53, the estimated RR was 0.14 with 95% CI (0.03, 0.67).

Table 22. Adjudicated Acute Pancreatitis Event Rate Between Pooled Olezarsen and Pooled Placebo, Subset of Patients With ≥ 2 Adjudicated Acute Pancreatitis Events in 5 years Prior to Enrollment, Full Analysis Set

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Olezarsen N=43	Pooled Placebo N=23
Patients with ≥ 2 adjudicated acute pancreatitis events in 5 years prior to enrollment	6	6	12	9
Week 1 to Week 53				
Patients with events, n (%)	1 (16.7)	1 (16.7)	2 (16.7)	6 (66.7)
Number of events	1	1	2	10
Total patient years	5.5	6.1	11.7	8.7
Mean event rate/100 patient years (95% CI)			16.59 (4.05, 67.95)	118.59 (61.23, 229.70)
Mean rate ratio: olezarsen/placebo			0.14 (0.03, 0.67)	

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Pooled Olezarsen N=43	Pooled Placebo N=23
Week 13 to Week 53				
Patients with events, n (%)	1 (16.7)	1 (16.7)	2 (16.7)	5 (55.6)
Number of events	1	1	2	7
Total patient years	4.1	4.8	8.9	6.6
Mean event rate/100 patient years (95% CI)			21.36 (5.23, 87.22)	106.91 (50.20, 227.68)
Mean rate ratio: olezarsen/placebo			0.20 (0.04, 0.99)	

Source: Statistical Reviewer's Analysis; adsl.xpt, adadj.xpt; t678354cs3_14_2_2_5_2_premodel.xpt; t678354cs3_14_2_2_6_2_premodel.xpt

Note: The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.

Abbreviations: CI, confidence interval; N, total number of subjects

A post hoc analysis of the proportion of subjects in the *single* treatment arm olezarsen 80 mg who had an event of adjudicated AP from Week 1 to 53 was conducted in the FAS ([Table 23](#)), in the subset of patients with a prior history of pancreatitis within 10 years prior to screening ([Table 24](#)), and in the subset of patients with two or more events of AP in 5 years prior to enrollment versus placebo ([Table 25](#)).

For the olezarsen 80 mg group, a nominally significant decrease in the proportion of patients experiencing an event of AP from Week 1 to 53, compared with the placebo group, was observed for all patients (nominal p-value = 0.0470) and for patients with a prior history of pancreatitis within 10 years prior to screening (nominal p-value = 0.0133), while the decrease in proportion for patients with two or more events of adjudicated pancreatitis in 5 years prior to enrollment did not reach nominal significance (nominal p-value = 0.1189).

[Table 23](#) displays the results for the adjudicated AP event rates between single treatment arm of 80 mg olezarsen and pooled placebo in the FAS population for Week 1 to 53 and Week 13 to 53. Only one event occurred in the olezarsen 80 mg group and 11 events in the pooled placebo group from Week 1 to 53. There was an 86% decrease in the adjudicated pancreatitis event rate for the pooled olezarsen group compared to the pooled placebo group from Week 1 to 53, the estimated RR was 0.14 with 95% CI (0.01, 1.30).

Table 23. Ad Hoc Analysis: Adjudicated Acute Pancreatitis Event Rate Between 80 mg Olezarsen and Pooled Placebo, Full Analysis Set

Parameter	Olezarsen 80 mg N=22	Pooled Placebo N=23
Week 1 to Week 53		
Patients with events Week 1 to Week 53, n (%)	1 (4.5)	7 (30.4)
Number of events	1	11
Total patient years	20.3	40.2
Mean event rate/100 patient years (95% CI)	4.93 (0.62, 39.18)	36.07 (14.42, 90.21)
Mean rate ratio: olezarsen/placebo	0.14 (0.01, 1.30)	

Parameter	Olezarsen 80 mg N=22	Pooled Placebo N=23
Week 13 to Week 53		
Patients with events Week 13 to Week 53, n (%)	1 (4.5)	6 (26.1)
Number of events	1	8
Total patient years	16.2	17.6
Mean event rate/100 patient years (95% CI)	5.71 (0.74, 44.10)	33.39 (13.22, 84.34)
Mean rate ratio: olezarsen/placebo	0.17 (0.02, 1.53)	

Source: Statistical Reviewer's Analysis; adsl.xpt, adadj.xpt; t678354cs3_14_2_2_5_2_premodel.xpt; t678354cs3_14_2_2_6_2_premodel.xpt

Note: The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.

Abbreviations: CI, confidence interval; N, total number of subjects

[Table 24](#) displays the results for the adjudicated AP event rates between 80 mg olezarsen and pooled placebo in the subset FAS population with a prior history of pancreatitis within 10 years prior to screening for Week 1 to 53 and Week 13 to 53. Only one event occurred in the olezarsen 80 mg group and 11 events in the pooled placebo group from Week 1 to 53. There was a 90% decrease in the adjudicated pancreatitis event rate for the pooled olezarsen group compared to the pooled placebo group from Week 1 to 53, the estimated RR was 0.10 with 95% CI (0.01, 0.87).

Table 24. Ad Hoc Analysis: Adjudicated Acute Pancreatitis Event Rate Between 80 mg Olezarsen and Pooled Placebo Subjects With a Prior History of Pancreatitis Within 10 Years Prior to Screening, Full Analysis Set

Parameter	Olezarsen 80 mg N=22	Pooled Placebo N=23
Patients with a prior history of pancreatitis within 10 years prior to screening	16	15
Week 1 to Week 53		
Patients with events Week 1 to Week 53, n(%)	1 (6.3)	7 (46.7)
Number of events	1	11
Total patient years	15.6	29.3
Mean event rate/100 patient years (95% CI)	6.73 (0.90, 50.21)	66.65 (30.81, 144.15)
Mean rate ratio: olezarsen/placebo	0.10 (0.01, 0.87)	

Parameter	Olezarsen	Pooled Placebo
	80 mg N=22	N=23
Week 13 to Week 53		
Patients with events week 13 to week 53, n(%)	1 (6.3)	6 (40.0)
Number of events	1	8
Total patient years	11.9	11.3
Mean event rate/100 patient years (95% CI)	8.41 (1.16, 61.03)	58.83 (26.01, 133.05)
Mean rate ratio: olezarsen/placebo	0.14 (0.02, 1.19)	

Source: Statistical Reviewer's Analysis; adsl.xpt, adadj.xpt; t678354cs3_14_2_2_5_2_premodel.xpt; t678354cs3_14_2_2_6_2_premodel.xpt

Note: The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Negative Binomial model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate for Week 1 to Week 53. The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Poisson regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate for Week 13 to Week 53. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.
 Abbreviations: CI, confidence interval; N, total number of subjects

[Table 25](#) displays the results for the adjudicated AP event rates between 80 mg olezarsen and pooled placebo in the subset FAS population with at least two adjudicated AP events in 5 years prior to enrollment for Week 1 to 53 and Week 13 to 53. Only one event occurred in the olezarsen 80 mg group and six events in the pooled placebo group from Week 1 to 53. There was an 86% decrease in the adjudicated pancreatitis event rate for the pooled olezarsen group compared to the pooled placebo group from Week 1 to 53, the estimated RR was 0.14 with 95% CI (0.02, 1.14).

Table 25. Ad Hoc Analysis: Adjudicated Acute Pancreatitis Event Rate Between 80 mg Olezarsen and Pooled Placebo in the Subset of Patients With ≥2 Adjudicated Acute Pancreatitis Events in 5 Years Prior to Enrollment, Full Analysis Set

Parameter	Olezarsen	Pooled Placebo
	80 mg N=22	N=23
Patients with ≥2 adjudicated acute pancreatitis events in 5 years prior to enrollment	6	9
Week 1 to Week 53		
Patients with events Week 1 to Week 53, n (%)	1 (16.7)	6 (66.7)
Number of events	1	10
Total patient years	6.1	8.7
Mean event rate/100 patient years (95% CI)	16.29 (2.19, 121.27)	118.59 (61.24, 229.67)
Mean rate ratio: olezarsen/placebo	0.14 (0.02, 1.14)	
Week 13 to Week 53		
Patients with events Week 13 to Week 53, n (%)	1 (16.7)	5 (55.6)
Number of events	1	7
Total patient years	4.8	6.6
Mean event rate/100 patient years (95% CI)	22.96 (3.15, 167.60)	106.72 (50.02, 227.72)
Mean rate ratio: olezarsen/placebo	0.22 (0.03, 1.85)	

Source: Statistical Reviewer's Analysis; adsl.xpt, adadj.xpt; t678354cs3_14_2_2_5_2_premodel.xpt; t678354cs3_14_2_2_6_2_premodel.xpt

Note: The mean rate and 95% CI for each treatment group, mean rate ratio and its 95% CI and p-value were estimated from a Negative Binomial regression model with the treatment group and previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The period of 5 years prior to enrollment spans from 1826 days before the first dose date and up to the first dose date and time.

Abbreviations: CI, confidence interval; N, total number of subjects

There were a few differences in the initial adjudication report by the AP reviewers.

- Placebo group Subject ID# (b) (6): one classified as pancreatitis, one classified as not pancreatitis; final meeting was classified as documented pancreatitis.
- Placebo group Subject ID# (b) (6): one classified as documented, one classified as probable; however; final meeting was classified as documented.
- Placebo group Subject ID# (b) (6) and ID# (b) (6): one classified as not documented, one classified as insufficient; both cases were negative for an adjudicated event.
- Olezarsen 80 group Subject ID# (b) (6): one classified as not documented, one classified as insufficient; final meeting decision was negative for an adjudicated event.

[Table 26](#) shows the demographics of subjects with prospectively confirmed adjudicated AP. The subjects with confirmed prospective AP in Study CS3 were relatively young, with a mean age of 44.8 years, but with an age range that was broad from 32-69 years. There were more females than males who had adjudicated pancreatitis in this study. All the subjects had a history of a previous AP event within the last 5 years with a range from 2 to 16 prior events. The baseline TG ranged from 1355 to 6116 mg/dL.

Table 26. Demographics of Subjects With Prospectively Positively Adjudicated Acute Pancreatitis, Trial CS3

Treatment Group/ Subject ID	Age	Sex	Race	Number of AP Events in 5 Years Prior	Study Day of AP Event	Baseline TG (mg/dL)	Last TG Before AP Event (mg/dL)
Olezarsen 80 mg/ ID# (b) (6)	38	Female	Asian	2	357	6116	1806
Olezarsen 50 mg/ ID# (b) (6)	38	Female	White	4	102	1651	1876
Placebo/ ID# (b) (6)	47	Female	Other	3	100 120 148	1976	1450 3830 3830
Placebo/ ID# (b) (6)	32	Male	White	1	341	2649.5	4192
Placebo/ ID# (b) (6)	39	Female	White	3	93	1354.5	2806
Placebo/ ID# (b) (6)	46	Female	White	16	343	2123.5	3265
Placebo/ ID# (b) (6)	54	Female	White	2	175	3605	3968
Placebo/ ID# (b) (6)	41	Male	White	4	22	3616.5	4389
Placebo/ ID# (b) (6)	69	Female	White	3	9 24 330	4420.5	4615 4615 4417

Source: Applicant response to an information request submitted 7.26.2024.
Abbreviations: AP, acute pancreatitis; TG, triglycerides

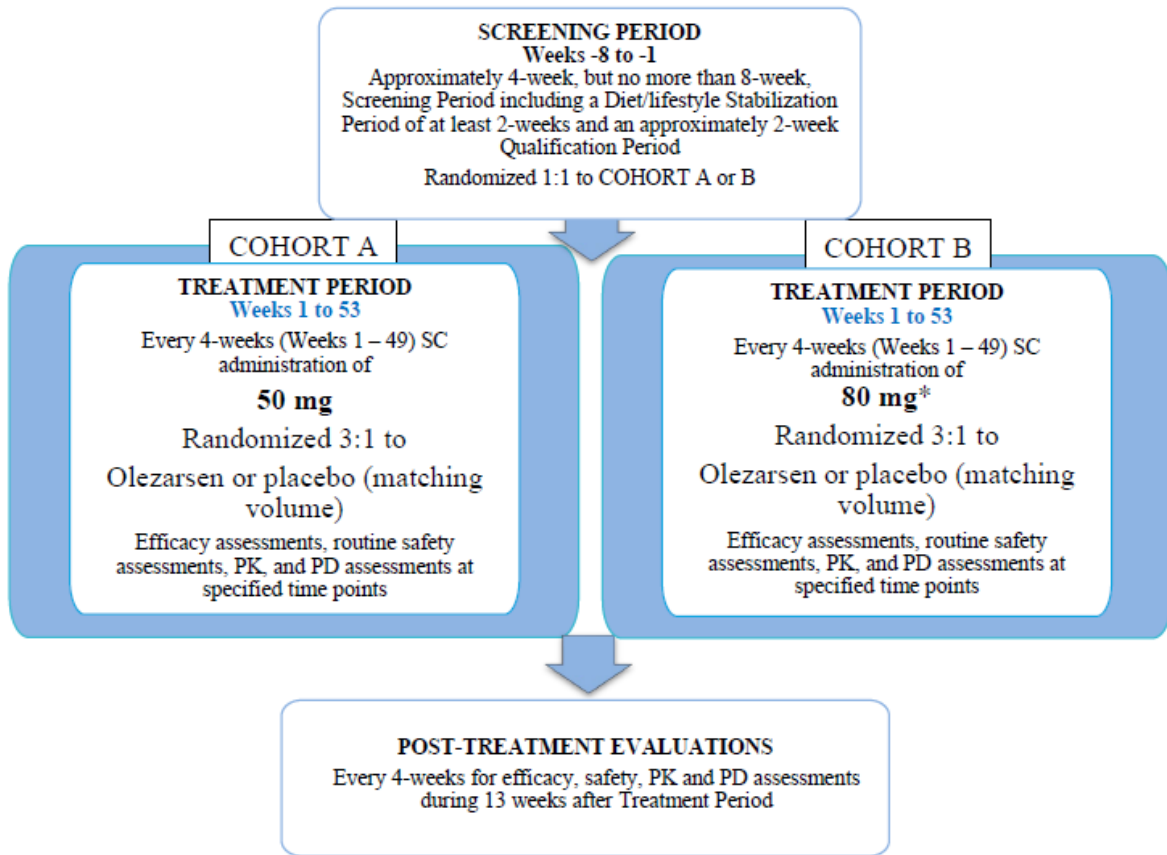
Regarding the two subjects who had adjudicated pancreatitis on the olezarsen treatment arms, Subject ID# (b) (6) (olezarsen 80 mg), the subject had a large reduction in TG from 6116 to 1806 mg/dL, but for the subject receiving olezarsen 50 mg, the TG slightly increased from baseline 1651 mg/dL to 1876 mg/dL, the last TG before the AP event. Therefore, the degree of TG reduction did not necessarily correspond to AP risk reduction.

6.2.3. Trial ISIS-678354-CS8

6.2.3.1. Design, Trial CS8

The confirmatory phase 2 Trial ISIS 678354-CS8 (Trial CS8) was a randomized, double blind, placebo-controlled trial in patients with sHTG and moderate HTG with increased risk for or established CVD. The primary objective of this trial was to demonstrate the efficacy of olezarsen (two different doses) on the percent change in fasting TG over a 53-week period compared to placebo.

Figure 10. Study Design, Trial CS8



Source: Complete Study Report, Trial CS8
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous

The primary efficacy endpoint was the change from baseline to Month 6 (defined as the average of Weeks 25 and 27). The primary endpoint family included analysis of the percent change in fasting TG from baseline at Month 6 first for the olezarsen 80 mg group, and, if the comparison with placebo was statistically significant for the olezarsen 80 mg group, then analysis of the percent change in fasting TG from baseline at Month 6 for the olezarsen 50 mg group was to be determined.

The first 10 secondary endpoints are listed in order of hierarchy by priority of analysis. Refer to the Section [III](#) for the complete list.

- Secondary endpoint 1: Comparison of percent change in fasting TG from baseline at Month 12 between olezarsen 80 mg and pooled placebo in FAS
- Secondary endpoint 2: Comparison of percent change in fasting TG from baseline at Month 12 between olezarsen 50 mg and pooled placebo in FAS
- Secondary endpoint 3: Comparison of percent change in fasting ApoC-III from baseline at Month 6 between olezarsen 80 mg and pooled placebo in FAS
- Secondary endpoint 4: Comparison of percent change in fasting ApoC-III from baseline at Month 12 between olezarsen 80 mg and pooled placebo in FAS
- Secondary endpoint 5: Comparison of percent change in fasting ApoC-III from baseline at Month 6 between olezarsen 50 mg and pooled placebo in FAS
- Secondary endpoint 6: Comparison of percent change in fasting ApoC-III from baseline at Month 12 between olezarsen 50 mg and pooled placebo in FAS
- Secondary endpoint 7: Comparison of proportion of patients who achieve fasting TG <150 mg/dL at Month 6 between olezarsen 80 mg and pooled placebo in the subgroup of FAS with baseline fasting TG <500 mg/dL
- Secondary endpoint 8: Comparison of proportion of patients who achieve fasting TG <150 mg/dL at Month 12 between olezarsen 80 mg and pooled placebo in the subgroup of FAS with baseline fasting TG <500 mg/dL
- Secondary endpoint 9: Comparison of percent change in fasting very low-density lipoprotein cholesterol (VLDL-C) from baseline at Month 6 between olezarsen 80 mg and pooled placebo in FAS
- Secondary endpoint 10: Comparison of percent change in fasting VLDL-C from baseline at Month 12 between olezarsen 80 mg and pooled placebo in FAS

Comparison of adjudicated AP event rate between pooled olezarsen treatment group and placebo in FAS was listed as secondary endpoint #47. Acute pancreatitis was adjudicated by a blinded independent committee according to the Atlanta Classification and as outlined in the Pancreatitis Charter. Additional exploratory/safety endpoint for MACE was also explored.

6.2.3.2. Eligibility Criteria, Study Trial CS8

Main Inclusion Criteria

1. Aged ≥ 18 years at the time of informed consent
2. Was included in at least one of the following groups (a or b):

Hypertriglyceridemia with fasting TG ≥ 150 mg/dL and < 500 mg/dL with either

Clinical diagnosis of ASCVD defined as documented coronary artery disease, cerebrovascular disease, or peripheral artery disease

At increased risk of developing ASCVD defined as the following:

1. Type 2 diabetes mellitus,
2. Two (2) or more of the following cardiovascular (CV) risk-enhancing factors
 - a. Males ≥ 55 years of age or females ≥ 65 years of age
 - b. Females with a history of preeclampsia, or premature menopause
 - c. Family history of premature ASCVD
 - d. Current tobacco use (5 cigarettes/day or more for at least 1 year)
 - e. Metabolic syndrome
 - f. Hypertension requiring antihypertensive treatment
 - g. Chronic kidney disease stage 3 (eGFR 30-59 mL/min/m²)
 - h. LDL-C ≥ 160 mg/dL
 - i. LDL-C ≥ 100 mg/dL on therapy to lower LDL-C
 - j. Elevated high-sensitivity C-reactive protein (hsCRP) (≥ 2.0 mg/L)
 - k. Elevated lipoprotein (≥ 50 mg/dL)
 - l. Ankle-brachial index < 0.9 in asymptomatic patients
 - m. Coronary artery calcium score ≥ 100

Severe HTG with fasting TG ≥ 500 mg/dL

3. Patients were to be on standard of care lipid-lowering medications per local guidelines. Lipid-lowering medications were to be optimized and stabilized for at least 4 weeks prior to screening to minimize changes in these medications during the study.
4. Patients were to be willing to comply with diet and lifestyle recommendations
5. Satisfied the following:

Females could not be pregnant or lactating, and had to be either:

Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)

Postmenopausal (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 levels in the postmenopausal range for the laboratory involved)

Abstinent*

If engaged in sexual relations of childbearing potential, had to 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)

Males had to be surgically sterile, abstinent*, or if engaged in sexual relations with a female of childbearing potential, were to utilize 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 was only acceptable as true abstinence (i.e., when this was 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 were not acceptable methods of contraception.*

Key Exclusion Criteria

1. Diabetes with any of the following

Newly diagnosed within 12 weeks of screening

Glycosylated hemoglobin (HbA1c) $\geq 9.5\%$ at screening

Change in basal insulin regimen $> 20\%$ within 3 months prior to screening

For patients with type 1 diabetes: episode of diabetic ketoacidosis, or three or more episodes of severe hypoglycemia within 6 months prior to screening

2. Acute coronary syndrome or stroke/transient ischemic attack within 6 months prior to screening

3. Major surgery, peripheral revascularization, or non-urgent percutaneous coronary intervention 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 have rendered a patient unsuitable for inclusion:

ALT or AST $> 3.0 \times$ ULN

Total bilirubin $> 1.5 \times$ ULN unless due to Gilbert's syndrome

eGFR < 30 mL/min/1.73 m² (as determined by the Chronic Kidney Disease Epidemiology formula for creatinine clearance;

UPCR ≥ 500 mg/g

6. Uncontrolled arterial hypertension (BP $> 180/100$ mmHg) despite antihypertensive therapy

7. Uncontrolled hypothyroidism, such as thyroid-stimulating hormone $> 1.5 \times$ ULN and free thyroxine $<$ lower limit of normal, clinical evidence of hypothyroidism, or thyroid hormone therapy that had not been stable for ≥ 4 weeks prior to screening

8. Active infection with human immunodeficiency virus, 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 tested positive by serology (for example,

positive for Hepatitis C antibody), but negative by RNA may have been allowed in consultation with the Sponsor Medical Monitor or designee

9. 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 had been successfully treated.
10. Hypersensitivity to the active substance or to any of the excipients (olezarsen or placebo)
11. Concomitant medication/procedure restrictions

Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening and during the study unless approved by the Sponsor Medical Monitor or designee

Use of bile acid resins such as colestipol, cholestyramine, or colesevelam within 4 weeks prior to screening or planned during the study

Plasma apheresis within 4 weeks prior to screening or planned during the study

Change in medications known to exacerbate HTG such as certain beta blockers, thiazides, isotretinoin, oral antidiabetic medications, tamoxifen, estrogens, or progestins within 4 weeks prior to screening

Change in atypical antipsychotic medications (e.g., olanzapine and clozapine) within 3 months prior to screening

The eligibility criteria for Trial CS8 were acceptable.

6.2.3.3. Patient Screening and Disposition, Trial CS8

A total of 304 subjects were screened for Trial CS8. Of those screened, approximately 49% failed screening due mostly to failure to meet inclusion or exclusion criteria (n=144); other (n=3); withdrawal of consent (n=3).

Table 27. Subject Screening and Enrollment, Trial CS8

Disposition	Trial ISIS-678354-CS8
Patients screened	304
Screening failures	150
Inclusion/exclusion	144
Other	3
Withdrawal of consent	3
Patients enrolled	304
Patients randomized	154

Source: Clinical Analyst; ds.xpt and Clinical Study Report; Software: R

A total of 154 subjects were randomized to receive olezarsen (olezarsen 80 mg, n=57, olezarsen 50 mg, n=58) or placebo (n=39). Approximately 81% or 94/115 subjects in the pooled olezarsen treatment group completed the trial. [Table 28](#) below summarizes the disposition of subjects by treatment arm.

Overall, 18% or 21/115 subjects discontinued pooled olezarsen treatment (14 subjects in the olezarsen 50 mg group, 7 subjects in the olezarsen 80 mg group) compared to 8% or 3 subjects in the placebo group.

Of those that discontinued study drug treatment, 13 subjects in the pooled olezarsen group discontinued (10 subjects in the olezarsen 50 mg group and 3 subjects in the olezarsen 80 mg

group) due the study drug due to an AE; 1 subject in the placebo group discontinued treatment due to an AE.

Table 28. Subject Disposition, Trial CS8

Disposition Outcome	Olezarsen 50 mg N=58 n (%)	Olezarsen 80 mg N=57 n (%)	Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Patients randomized	58	57	39	NA	NA
Per-protocol population	49	50	38	NA	NA
Safety population	58	57	39	NA	NA
Study treatment termination	58 (100)	57 (100)	39 (100)	0.0 (-6.3, 9.1)	0.0 (-6.4, 9.1)
Completed	44 (75.9)	50 (87.7)	36 (92.3)	-16.4 (-30.4, -1.1) *	-4.6 (-17.1, 9.6)
Discontinued study drug	14 (24.1)	7 (12.3)	3 (7.7)	16.4 (1.1, 30.4) *	4.6 (-9.6, 17.1)
Adverse event	10 (17.2)	3 (5.3)	1 (2.6)	14.7 (2.3, 26.9) *	2.7 (-8.5, 12.3)
Other	2 (3.4)	3 (5.3)	0	3.4 (-5.7, 11.8)	5.3 (-4.0, 14.4)
Withdrawal by subject	2 (3.4)	1 (1.8)	2 (5.1)	-1.7 (-13.9, 7.5)	-3.4 (-15.4, 4.9)

Source: Clinical Analyst ds.xpt and adsl.xpt; Software: R

Duration is up to 374 days. Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; n, number of patients in specified population or group; N, number of patients in treatment arm; NA, not applicable

6.2.3.4. Patient Demographics, Trial CS8

[Table 29](#) provides the demographics and baseline characteristics for the subjects enrolled in Trial CS8. There are no significant differences in these baseline characteristics between treatment or placebo arms.

Table 29. Baseline Demographics and Clinical Characteristics, Trial CS8

Characteristic	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Placebo N=39
Sex, n (%)			
F	24 (41.4)	17 (29.8)	24 (61.5)
M	34 (58.6)	40 (70.2)	15 (38.5)
Age, years			
Mean (SD)	62.3 (10.1)	60.4 (10.8)	63.3 (9.5)
Median (min, max)	63 (38, 83)	60 (35, 83)	63 (46, 83)
<40 years	1 (1.7)	2 (3.5)	0
≥40 to <65 years	32 (55.2)	32 (56.1)	23 (59.0)
≥65 years	25 (43.1)	23 (40.4)	16 (41.0)
Age group ≥75, years, n (%)			
≥75	9 (15.5)	4 (7.0)	6 (15.4)
Baseline BMI group, n (%)			
≥18.5 to ≤25 BMI	1 (1.7)	5 (8.8)	1 (2.6)
>25 to ≤30 BMI	15 (25.9)	14 (24.6)	7 (17.9)
>30 BMI	42 (72.4)	38 (66.7)	31 (79.5)
Baseline weight (kg) group, n (%)			
≥50 to <65 Kg	2 (3.4)	5 (8.8)	1 (2.6)
≥65 Kg	56 (96.6)	52 (91.2)	38 (97.4)

NDA 218614
Tryngolza (olezarsen sodium)

Characteristic	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Placebo N=39
Diabetic status, n (%)			
No	21 (36.2)	19 (33.3)	9 (23.1)
Yes	37 (63.8)	38 (66.7)	30 (76.9)
Cardiac related history, n (%)			
ASCVD			
No	44 (75.9)	45 (78.9)	34 (87.2)
Yes	14 (24.1)	12 (21.1)	5 (12.8)
Stroke			
No	55 (94.8)	57 (100)	38 (97.4)
Yes	3 (5.2)	0	1 (2.6)
TIA			
No	54 (93.1)	55 (96.5)	38 (97.4)
Yes	4 (6.9)	2 (3.5)	1 (2.6)
Coronary artery disease			
Yes	12 (20.7)	10 (17.5)	5 (12.8)
Missing	46 (79.3)	47 (82.5)	34 (87.2)
CABG			
No	53 (91.4)	51 (89.5)	37 (94.9)
Yes	5 (8.6)	6 (10.5)	2 (5.1)
Myocardial infarction			
No	51 (87.9)	51 (89.5)	36 (92.3)
Yes	7 (12.1)	6 (10.5)	3 (7.7)
Percutaneous coronary intervention			
No	51 (87.9)	52 (91.2)	34 (87.2)
Yes	7 (12.1)	5 (8.8)	5 (12.8)
Heart failure			
No	54 (93.1)	55 (96.5)	37 (94.9)
Yes	4 (6.9)	2 (3.5)	2 (5.1)
Race, n (%)			
Asian	1 (1.7)	0	0
Black or African American	3 (5.2)	5 (8.8)	5 (12.8)
White	54 (93.1)	52 (91.2)	34 (87.2)
Ethnicity, n (%)			
Hispanic or Latino	21 (36.2)	23 (40.4)	13 (33.3)
Not Hispanic or Latino	37 (63.8)	34 (59.6)	26 (66.7)
Country of participation, n (%)			
Canada	3 (5.2)	1 (1.8)	4 (10.3)
United States	55 (94.8)	56 (98.2)	35 (89.7)
Is in US, n (%)			
US	55 (94.8)	56 (98.2)	35 (89.7)
Non-US	3 (5.2)	1 (1.8)	4 (10.3)

Source: Clinical Analyst adsl.xpt; Software: R

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; F, female; M, male; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation; US, United States

[Table 30](#) summarizes the lipids and lipoprotein at baseline for Trial CS8.

Table 30. Summary of Baseline Triglycerides, Other Lipid, and Lipoprotein Panel, Full Analysis Set, Trial CS8

Baseline Characteristics/ Statistic	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Placebo N=39
Triglycerides (mg/dL)			
Mean (SD, SEM)	292.1 (183.0, 24.0)	315.1 (221.6, 29.4)	302.1 (201.9, 32.3)
Median (P25, P75)	230.0 (182.5, 331.5)	241.5 (179.5, 357.5)	249.3 (219.5, 284.5)
Minimum, maximum	141, 1181	133, 1269	152, 1277
ApoC-III (mg/dL)			
Mean (SD, SEM)	16.8 (7.4, 1.0)	15.8 (6.7, 0.9)	16.9 (5.6, 0.9)
Median (P25, P75)	15.3 (12.0, 19.3)	13.4 (11.5, 18.0)	15.3 (13.2, 18.7)
Minimum, maximum	8, 57	7, 37	10, 37
Total cholesterol (mg/dL)			
Mean (SD, SEM)	176.3 (37.9, 5.0)	179.3 (53.4, 7.1)	182.4 (47.5, 7.6)
Median (P25, P75)	175.5 (147.5, 206)	168 (147.0, 193.0)	185 (146.0, 209.5)
Minimum, maximum	105, 262	103, 407	110, 326
HDL-C (mg/dL)			
Mean (SD, SEM)	41.9 (14.3, 1.9)	39.5 (11.7, 1.6)	43.4 (13.5, 2.2)
Median (P25, P75)	39.5 (32.0, 48.5)	36.5 (30.5, 47.5)	41.5 (34.0, 52.0)
Minimum, maximum	21, 82	22, 72	17, 75
ApoB (mg/dL)			
Mean (SD, SEM)	93.2 (24.6, 3.2)	96.2 (27.0, 3.6)	96.8 (24.8, 4.0)
Median (P25, P75)	90.8 (75.5, 105.0)	93.0 (78.0, 107.0)	94.0 (78.0, 114.5)
Minimum, maximum	46, 153.5	45, 177	53, 187
VLDL-C (mg/dL)			
Mean (SD, SEM)	49.9 (24.2, 3.2)	54.3 (42.2, 5.6)	50.3 (20.2, 3.2)
Median (P25, P75)	41.0 (34.0, 62.5)	43.0 (31.0, 56.7)	41.5 (36.0, 61.0)
Minimum, maximum	20, 154	15, 261	29, 112
Non-HDL-C (mg/dL)			
Mean (SD, SEM)	134.4 (37.3, 4.9)	139.7 (52.1, 6.9)	139.0 (42.7, 6.8)
Median (P25, P75)	132.3 (103.5, 156.5)	126 (110.0, 150.5)	134.5 (110.0, 161.5)
Minimum, maximum	76, 237	70, 354	81, 281
LDL-C (mg/dL)			
Mean (SD, SEM)	84.5 (32.7, 4.3)	85.5 (33.8, 4.5)	88.4 (35.3, 5.7)
Median (P25, P75)	83.8 (26.5, 106.0)	80.5 (62.0, 102.0)	81.5 (62.0, 104.5)
Minimum, maximum	19, 155	38, 216	31, 209

Source: Statistical Reviewer

Abbreviations: Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P25, 25th percentile; P75, 75th percentile; SD, standard deviation; SEM, standard error of the mean; VLDL-C, very low-density lipoprotein cholesterol

Baseline TG, other lipids, and lipoprotein levels for the FAS were similar across all treatment groups. Mean fasting TG levels at baseline were 315.1, 292.1, and 302.1 mg/dL for the olezarsen 80 mg group, olezarsen 50 mg group, and placebo group, respectively. Median baseline TG levels were between 230 and 250 mg/dL in all treatment groups. Mean fasting ApoC-III levels at baseline were 15.747 mg/dL, 16.747 mg/dL, and 16.878 mg/dL for the olezarsen 80 mg, olezarsen 50 mg, and placebo treatment groups, respectively.

6.2.3.5. Statistical Analysis Plan, Trial CS8

Analysis Population

The FAS was defined as all patients who were randomly assigned to treatment and received any amount of olezarsen or placebo. The primary efficacy analysis was performed using the FAS. The safety set was also defined as all patients who were randomized to treatment and received any amount of olezarsen or placebo. The safety analysis was performed using the safety set.

Primary Efficacy Analysis

The primary analysis time point was at Month 6. The value of the primary endpoint was defined as the average of Weeks 25 and 27 fasting assessments. The Applicant's prespecified primary analysis of the primary endpoint, the mean percent change in fasting TG from baseline to the primary analysis time point, was performed using an ANCOVA model that assumes unequal variance with missing values imputed using the retrieved dropout method (patients who discontinue treatment before Week 25 but still have TG assessments at Weeks 25 or 27). For Month 12 the retrieved dropout method includes patients who discontinue treatment before Week 51 but still have TG assessments at Weeks 51 or 53. The model included treatment group (olezarsen 80 mg, olezarsen 50 mg, pooled placebo) as the fixed effect and natural log-transformed baseline fasting TG as a covariate.

Missing Data

There was about 7.1% missing data at Month 6 (five patients in olezarsen 50 mg, five patients in olezarsen 80 mg, and one patient in the placebo group). If there was not a sufficient number of retrieved dropouts, the missing TG data was imputed using a wash-out multiple imputation approach (J2R). The Applicant stated that patients treated with olezarsen who had 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 had missing TG values multiply imputed based on baseline fasting TG and fasting TG values at postbaseline visits from the placebo group.

The Applicant selected the first 100 imputed datasets with the imputed values falling into feasible range of the imputed endpoints among 1000 imputations. This procedure may underestimate the uncertainty of the imputed values. FDA conducted a washout imputation in the primary analysis to impute missing data without truncating any imputed values. FDA results are shown in Section [6.2.3.6](#). The FDA results shown are different from the Applicant's results, but the outcomes concur.

The Applicant conducted some sensitivity analyses in the FAS population to evaluate the impact of missing data on the analysis conclusion for the primary endpoint. The primary analysis was repeated using the completers set, which is all observed data (no missing data imputation). A nonparametric analysis with Wilcoxon rank-sum test, a 2-dimensional tipping-point analysis, on the FAS population, a pattern mixture models with ANCOVA was conducted, and an ANCOVA model using log-transformed data in the FAS population.

Secondary Endpoints

There are many secondary endpoints (see Section III). This review will show the secondary endpoints, percent change in fasting TG from baseline at Month 12, the percent change in fasting non-HDL-C, HDL-C, LDL-C, total Apo from baseline at Month 6 and 12 and adjudicated AP event rate during the treatment period. The Month 12 value was defined as the average of Weeks 51 and 53 values of the endpoint. The Applicant's prespecified continuous secondary endpoints were analyzed using an ANCOVA model that assumes unequal variance with missing values imputed using the retrieved dropout method. The model included treatment group (olezarsen 80 mg, olezarsen 50 mg, pooled placebo) as the fixed effect and natural log-transformed baseline fasting TG as a covariate for mean percent change in fasting TG from baseline to Month 12. For the percent change in fasting non-HDL-C, HDL-C, LDL-C, and total Apo from baseline to Month 6 and 12 were analyzed using an ANCOVA model that assumes unequal variance with missing values imputed using the retrieved dropout method. The model included treatment group (olezarsen 80 mg, olezarsen 50 mg, pooled placebo) baseline stratification factor (qualification fasting TG levels of <500 mg/dL vs. ≥500 mg/dL) as the fixed effect and natural log-transformed baseline fasting associated endpoint as a covariate.

Adjudicated AP event rate: The pancreatitis endpoint was analyzed using a negative binomial regression model or Poisson regression model with treatment group and natural log transformed baseline fasting TG as the factors, and number of adjudicated AP events in 5 years prior to the enrollment as a covariate. The logarithm of time in year that each patient was observed from Week 1 to 53 was used as an offset variable.

Multiplicity

A step-down procedure to account for multiplicity across treatment comparisons and key endpoints was used. All tests will be conducted at a two-sided alpha level of 0.05. For the primary endpoint family, the two treatment arms (olezarsen 80 mg and olezarsen 50 mg) were compared against pooled placebo using the hierarchical testing procedure, in which the olezarsen 80 mg treatment group was first compared to the pooled placebo at the 2-sided alpha level of 0.05. If the comparison was statistically significant ($p < 0.05$), then the olezarsen 50 mg treatment group was compared against the pooled placebo at the alpha level of 0.05. If the comparison of the olezarsen 80 mg treatment group was not statistically significant, then the comparison of the olezarsen 50 mg treatment group against pooled placebo and all secondary endpoints were considered exploratory.

Testing of the secondary endpoint family was performed only if the comparison of the primary endpoint was statistically significant ($p < 0.05$) for both the olezarsen 80 mg and 50 mg treatment groups.

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

6.2.3.6. Results of Analyses, Trial CS8

The primary analysis results for fasting TG at Month 6 are shown in [Table 31](#). A statistically significantly greater mean percent decrease in fasting TG levels from baseline at Month 6 was observed in both the olezarsen 80 mg and olezarsen 50 mg groups compared with the placebo group.

Table 31. Primary Analysis Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 6, Full Analysis Set, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Pooled Placebo N=39
Baseline mean (SD)	292.1 (183.0)	315.1 (221.6)	302.1 (201.9)
LS means (SD)	-59.5 (2.2)	-64.3 (2.4)	-8.0 (5.0)
Treatment difference, olezarsen-placebo	-51.7	-56.5	
95% CI	-62.5, -41.0	-67.4, -45.6	
P-value	<0.0001	<0.0001	

Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt

Month 6 was defined as the average of Weeks 25 and 27.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo) as a fixed effect and log-transformed Baseline triglyceride as a covariate. The ANCOVA model assumed unequal variance.

Missing data was imputed using Washout method.

Abbreviations: CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

Since both primary endpoints achieved superiority according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the second primary endpoint. [Table 32](#) shows the results for fasting TG at Month 12. Note that the results were in favor of both olezarsen groups, with the 80 mg group showing a greater mean decrease compared to pooled placebo.

Table 32. Secondary Analysis Percent Change in Baseline in Fasting Triglycerides (mg/dL) at Month 12, Full Analysis Set, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Pooled Placebo N=39
Baseline mean (SD)	292.1 (183.0)	315.1 (221.6)	302.1 (201.9)
LS means (SD)	-52.9 (4.0)	-59.6 (4.5)	-5.5 (3.8)
Treatment difference, olezarsen –placebo	-47.4	-54.1	
95% CI	-58.3, -36.5	-65.8, -42.5	

Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt

Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo) as a fixed effect and log-transformed Baseline triglyceride as a covariate. The ANCOVA model assumed unequal variance.

Missing data was imputed using Washout method.

Abbreviations: CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 33](#) shows the results for fasting non-HDL-C at Months 6 and 12. The mean percent decrease in fasting non-HDL-C levels from baseline at Months 6 and 12 are seen for both olezarsen groups.

Table 33. Secondary Endpoint: Percent Change in Baseline in Fasting Non-HDL-C(mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Pooled Placebo N=39
Baseline mean (SD)	134.4 (37.3)	139.7 (52.1)	139.0 (42.7)
Month 6			
LS means (SD)	-19.8 (3.0)	-17.4 (3.5)	7.2 (5.6)
Treatment difference, olezarsen -placebo	-26.9	-24.5	
95% CI	-39.4, -14.5	-37.6, -11.5	
Month 12			
LS means (SD)	-13.6 (4.3)	-19.6 (3.7)	4.5 (4.2)
Treatment difference, olezarsen -placebo	-18.1	-24.1	
95% CI	-29.8, -6.3	-35.1, -13.1	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefx.xpt

Month 6 was defined as the average of Weeks 25 and 27.

Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo) and Baseline stratification factor as a fixed effect and log-transformed Baseline Non-HDL-C as a covariate. The ANCOVA model assumed unequal variance.

Missing data was imputed using Washout method.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HDL-C, high-density-lipoprotein cholesterol; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 34](#) shows the results for fasting HDL-C at Months 6 and 12. Both olezarsen groups show an increase in fasting HDL-C compared to placebo.

Table 34. Secondary Endpoint: Percent Change in Baseline in Fasting HDL-C (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Pooled Placebo N=39
Baseline mean (SD)	41.9 (14.3)	39.5 (11.7)	43.4 (13.5)
Month 6			
LS Means (SD)	48.8 (4.9)	50.5 (4.1)	6.6 (3.0)
Treatment difference, olezarsen -Placebo	42.2	43.8	
95% CI	30.9, 53.4	33.8, 53.9	
Month 12			
LS Means (SD)	49.0 (5.2)	52.6 (5.1)	2.0 (3.1)
Treatment difference, olezarsen -Placebo	46.9	50.6	
95% CI	35.1, 58.8	38.7, 62.4	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefx.xpt

Month 6 was defined as the average of Weeks 25 and 27.

Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo) and Baseline stratification factor as a fixed effect and log-transformed Baseline HDL-C as a covariate. The ANCOVA model assumed unequal variance.

Missing data was imputed using Washout method.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 35](#) shows the results for fasting total ApoB at Months 6 and 12. Both olezarsen groups showed a decrease in total ApoB when compared to placebo.

Table 35. Secondary Endpoint: Percent Change in Baseline in Fasting Total ApoB (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Pooled Placebo N=39
Baseline mean (SD)	93.2 (24.6)	96.2 (27.0)	96.8 (24.8)
Month 6			
LS means (SD)	-14.0 (2.9)	-13.5 (2.7)	5.8 (4.6)
Treatment difference, olezarsen -placebo	-19.8	-19.3	
95% CI	-30.2, -9.4	-29.8, -8.8	
Month 12			
LS means (SD)	-11.0 (3.3)	-16.5 (2.9)	3.3 (3.8)
Treatment difference, olezarsen -placebo	-14.3	-19.7	
95% CI	-24.1, -4.5	-29.2, -10.3	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefl.xpt

Month 6 was defined as the average of Weeks 25 and 27.

Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo) and Baseline stratification factor as a fixed effect and log-transformed Baseline apoB as a covariate. The ANCOVA model assumed unequal variance.

Missing data was imputed using Washout method.

Abbreviations: ANCOVA, analysis of covariance; apoB, apolipoprotein B; CI, confidence interval; LS, least squares; N, total number of subjects; SD, standard deviation

[Table 36](#) shows the results for fasting LDL-C at Months 6 and 12. A decrease in fasting LDL-C is seen at Months 6 and 12 for both olezarsen groups when compared to placebo, but none are statistically significant.

Table 36. Secondary Endpoint: Percent Change in Baseline in Fasting LDL-C (mg/dL) at Months 6 and 12, Full Analysis Set, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Pooled Placebo N=39
Baseline mean (SD)	84.5 (32.7)	85.5 (33.8)	88.4 (35.3)
Month 6			
LS means (SD)	13.2 (5.2)	15.7 (5.5)	23.5 (7.3)
Treatment difference, olezarsen -placebo	-10.3	-7.8	
95% CI	-27.9, 7.3	-25.8, 10.2	
Month 12			
LS means (SD)	15.1 (5.6)	10.2 (5.4)	18.3 (6.0)
Treatment difference, olezarsen -placebo	-3.2	-8.1	
95% CI	-19.2, 12.9	-23.9, 7.8	

Source: Statistical Reviewer's Analysis; adsl.xpt, adefl.xpt

Month 6 was defined as the average of Weeks 25 and 27.

Month 12 was defined as the average of Weeks 51 and 53.

Note: LS Means are from the analysis of covariance model with treatment (olezarsen 80 mg, olezarsen 50 mg, placebo) and Baseline stratification factor as a fixed effect and log-transformed Baseline LDL-C as a covariate. The ANCOVA model assumed unequal variance.

Missing data was imputed using Washout method.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LDL-C, Low-density-lipoprotein Cholesterol; LS, least squares; N, total number of subjects; SD, standard deviation

There were no adjudicated AP events in this study. Thus, this endpoint was not analyzed.

6.3. Key Efficacy Review Issues

Issue/Background

The pivotal phase 3 trial in the FCS population, Trial CS3, assessed two primary co-endpoints, the mean percent change in fasting TG from baseline at Month 6 (average of Weeks 23, 25, and 27) for olezarsen 80 mg compared with placebo and the mean percent change in fasting TG from baseline at Month 6 for olezarsen 50 mg compared with placebo.

The primary TG endpoint was statistically significant for olezarsen 80 mg, but not for the olezarsen 50 mg dose. TG as an efficacy endpoint has been the basis of approval for other TG-lowering drugs in patients with severe hypertriglyceridemia (TG $\geq$ 500 mg/dL). TG has also been historically accepted by the Division as a surrogate for the reduction in the risk of AP. In addition to TG reduction, other lipid parameters were reviewed to determine whether the overall benefit risk profile remained favorable.

Trial CS3 also assessed key secondary endpoints of a reduction in prospectively adjudicated AP; it is the first outcome trial submitted to the Agency to measure adjudicated AP in an HTG population. The nominal finding of a reduction in the rate of AP is consistent with the pathophysiology that links elevated levels of TG with AP and the reduction of TG with a subsequent reduction in AP. However, the limitations of the trial are its small size and relatively short duration to determine AP outcomes.

The olezarsen FCS program was based on one adequate and well-controlled trial supported by confirmatory evidence generated by Trial CS8, a phase 2 trial in severe and moderate HTG populations.

6.3.1. Efficacy of Triglyceride Reduction of 80 mg Olezarsen in Trial CS3 in the FCS Population

Issue

Does the olezarsen 80 mg dose show efficacy in reducing TG levels in subjects with FCS in Trial CS3?

Background

Familial Chylomicronemia Syndrome

Familial chylomicronemia syndrome is a rare inherited disease of lipid metabolism that causes sHTG and hyperchylomicronemia and is estimated to affect 1 to 2 persons per 1,000,000 in the United States ([Warden et al. 2020](#); [Tripathi et al. 2021](#)). FCS is caused by reduced or absent LPL activity which leads to a reduced ability to clear TG leading to their accumulation in plasma. Because patients with FCS lack LPL activity, they are dependent on less efficient hepatic pathways for TG clearance. Genetic testing can confirm the diagnosis of FCS; however, FCS is often diagnosed using clinical signs and symptoms due to barriers to obtain genetic testing ([Moulin et al. 2018](#)).

The major complication of FCS is acute and recurrent episodes of pancreatitis. Approximately 85% of patients with FCS report at least one episode of AP, and 40% have multiple recurrences

during their lifetime ([Davidson et al. 2018](#)). In addition, patients with FCS frequently experience eruptive xanthomas, lipemia retinalis, nausea, vomiting, and recurrent abdominal pain ([Baass et al. 2020](#)).

Apolipoprotein C-III as a Target for Drug Development in Hypertriglyceridemia

ApoC-III is a small protein that inhibits the activity of LPL, the enzyme responsible for the break down and clearance of TG from the blood. ApoC-III also inhibits the uptake of TG-rich particles by the liver. Therefore, ApoC-III is a target for drug development aimed at lowering TG levels. Olezarsen is a GalNAc3-conjugated antisense oligonucleotide that reduces ApoC-III production by binding to *apoC-III* mRNA and inducing its degradation ([Alexander et al. 2019](#)).

TG Reduction Used in Other Drug Approvals in Hypertriglyceridemic Populations

TG has historically been accepted by the Division as the basis of approval for TG-lowering drugs in patients with sHTG (TG $\geq$ 500 mg/dL) and mixed dyslipidemia (TG $\geq$ 150-200 mg/dL). Moreover, elevated TG levels ($>$ 1,000 mg/dL) increase the risk of pancreatitis. The mechanism for hypertriglyceridemic pancreatitis is postulated to involve hydrolysis of TG by pancreatic lipase and release of free fatty acids that induce free radical damage, inflammation, and damage to the pancreas. Another hypothesis postulates that hyperviscosity due to elevated levels of chylomicrons in pancreatic capillaries leads to ischemia and pancreatitis ([Tsuang et al. 2009](#)). Since elevated TG levels are hypothesized to cause pancreatitis by these mechanisms, TG reduction has been assumed to decrease the risk for AP, although there have been no previous outcomes trials for AP in HTG populations.

Assessment

In Trial CS3, TG reduction (primary endpoint) was assessed as the difference in mean percent change from baseline to Month 6 in fasting TG between olezarsen 80 mg and pooled placebo in subjects with FCS in the FAS.

When deciding between using the median or the mean to describe changes in TG, the choice may depend on the distribution of the data, the clinical question of interest, and the consideration of influence of extreme large values. The mean is often the common choice as the difference in means estimate the average casual effect. The mean could be sensitive to extreme values (which may or may not be outliers). If there are outliers or if the distribution is highly skewed and the sample size is not large, inference on the mean relying on normal approximation might be suboptimal. If TG levels are highly variable with outliers, the median provides a better representation of the typical changes in TG. Previous studies indicate the typical distribution of TG is skewed. Recent TG lowering drugs (such as Vascepa and Epanova) and statins with TG lowering indications (Crestor, Lipitor) have used median percent TG changes as the primary endpoint as TG tends to have a skewed distribution (at least in non-FCS populations). The Applicant conducted a post hoc test for normality based on the observed data using a Shapiro-Wilk Normality Test. This test indicated that there was not enough evidence to conclude that the percent change in TG did not follow normal distribution. Thus, the Applicant used the difference in mean to describe the percent changes in TG.

A sensitivity analysis using a non-parametric Wilcoxon rank sum test was conducted to explore the impact of distributional assumption on the analysis conclusion. The median percent change in TG from baseline to Month 6 endpoint was -33.6% for olezarsen 80 mg, and +2.8% for

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placebo. The median of the treatment difference between olezarsen 80mg and placebo was -40.8% (95% CI -65.5, -16.1).

Another prespecified sensitivity analysis for the primary endpoint used a log transformation of TG data (Table 37). Testing was conducted to investigate whether the primary analysis was sensitive to violation of the normality assumption. These sensitivity analyses were consistently in favor of olezarsen 80 mg over placebo.

Table 37. Sensitivity Analysis: Percent Change From Baseline in Fasting Triglycerides (mmol/L) at Month 6, ANCOVA Model Using Log-Transformed Data, Full Analysis Set, Trial CS3

Parameter	Olezarsen	Olezarsen	Pooled Placebo N=23
	50 mg N=21	80 mg N=22	
Month 6 log transformed Month 6 to baseline ratio			
LSM	-0.20	-0.54	0.04
(95% CI)	(-0.45, 0.04)	(-0.79, -0.29)	(-0.19, 0.28)
% Change from baseline-100%*(back transformed Month 6 to baseline ratio - 1)			
LSM	-18.44	-41.67	4.31
(95% CI)	(-36.29, 4.41)	(-54.48, -25.25)	(-17.37, 31.68)
Ratio of active to placebo in original scale			
LSM	0.78	0.56	
(95% CI)	(0.56, 1.09)	(0.40, 0.78)	
Nominal p-value	0.1435	0.0005	

Source: Clinical Study Report- Trial ID: ISIS 678354-CS3 Table 14.2.1.1.17, pages 477-478

The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27.

Missing data after last dosing date for patients in the olezarsen arms were imputed using washout MI (J2R) approach. Missing data before the last dosing date or for patients in the placebo group were imputed under the MAR assumption. For each imputed data set, the percent change from Baseline to the primary analysis time point in fasting TG between each olezarsen treatment group (olezarsen 80 mg, olezarsen 50 mg) vs. pooled placebo are compared using ANCOVA model with log(y/x) as dependent variable, where y was the value of TG at primary analysis time point, x was the baseline value of TG; and the two randomization stratification factors and treatment group as factors and log-transformed baseline TG as a covariate. The model provided an estimate of log postbaseline to baseline ratio for each treatment group as well as the ratios relative to the pooled placebo group and the corresponding 95% confidence intervals (CIs).

Normality was tested based on observed data.

Note 1: The estimates from the 100 fitted models were combined to provide an overall estimate with corresponding confidence intervals and p-value.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; J2R, Jump to Reference; LSM, least squares mean; MI, multiple imputation; N, total number of subjects

The mean percent change in TG from baseline to Month 6 endpoint was -33.3% for olezarsen 80 mg, and +11.2% for placebo. The mean of the treatment difference between olezarsen 80 mg and placebo was -44.50% (95% CI -72.0, -17.0, p=0.0015).

Sensitivity analysis of the primary endpoint on the Per Protocol Set further confirmed the robustness of the results. Furthermore, the primary endpoint analysis was repeated in the FAS with no missing TG value at baseline and the primary analysis time point. This analysis also supported the conclusion from the primary analysis.

Additionally, the secondary endpoint of percent change in TG from baseline to Month 12 between olezarsen 80 mg and pooled placebo in subjects in the FAS showed persistence of TG reduction at Month 12. At Month 12, the placebo-subtracted mean percent decrease in TG for olezarsen 80 mg was approximately -61.4% (95% CI -101.9% to -20.8%).

Conclusion

Yes, the olezarsen 80 mg dose demonstrated efficacy in reducing TG levels in subjects with FCS in Trial CS3.

In the FCS population, who have severely elevated TG (typically >1,000 mg/dL, sometimes exceeding 2,000-10,000 mg/dL), the goal is to reduce TG levels as much as possible to minimize the risk of AP. Although there is no universally defined "target" TG level for patients with FCS, the general goal is to keep TG below 500 mg/dL. However, because FCS patients tend to have persistently high TG due to genetic factors, achieving levels below 1,000 mg/dL is often considered a success in clinical practice.

In Trial CS3, the placebo-subtracted mean percent change in TG (primary endpoint) showed a statistically significant mean TG reduction of -44%. In the olezarsen 80 mg group, the mean TG at baseline was 2613 mg/dL which decreased at Month 6 to a mean TG of 1732 mg/dL; the within treatment arm TG reduction with olezarsen 80 mg from baseline to Month 6 was approximately -33% (95% CI -49.03, -14.94). Therefore, olezarsen 80 mg dose showed both a statistically significant and clinically meaningful reduction in mean TG levels. Furthermore, this TG reduction is associated with a nominal reduction in the rate of AP (see Section [6.3.3](#)).

6.3.2.

(b) (4)

(b) (4)

6.3.3. Acceptability of the Secondary Endpoint of Acute Pancreatitis Risk Reduction

Issue

Is the secondary endpoint of reduction in the rate of AP acceptable and can it be described in the olezarsen labeling?

Background

As stated previously, patients with FCS have a significantly elevated risk of AP due to extremely high TG levels. Thirty to 40% of FCS patients will experience at least one episode of AP, and many will have recurrent, severe episodes that are potentially life-threatening. Estimates of the lifetime incidence of pancreatitis in this population range from approximately 50 to 80% ([Stroes et al. 2017](#)). Acute pancreatitis can lead to complications such as pancreatic necrosis, infection, and multiorgan failure.

Assessment

Trial CS3 investigated whether treatment with two different doses of olezarsen (80 mg and 50 mg) affected the rate of AP as compared to placebo in several secondary endpoints.

Because of the failure of efficacy (TG reduction) of olezarsen 50 mg dose (co-primary endpoint), all following endpoints, including AP rates, did not meet statistical significance but were considered to be of nominal significance. However, the reduction in the pancreatitis rate can be considered clinically significant. Note that the secondary endpoints summarized below regarding pancreatitis rate reduction considered the pooled treatment arms for both olezarsen 80 mg and olezarsen 50 mg.

Table 38. Summary of Key Acute Pancreatitis Secondary Efficacy Endpoints, Weeks 1 to 53, Trial CS3

Endpoint	Olezarsen 50 mg +		Nominal p-value
	Placebo N=23	Olezarsen 80 mg N=43	
Total 80 mg and 50 mg: adjudicated acute pancreatitis event rate from Week 1 to Week 53 – LSM event rate/100 patient years	36.31	4.37	0.0144
Total 80 mg and 50 mg (prior history of pancreatitis ≤10 years prior to screening): adjudicated acute pancreatitis event rate from Week 1 to Week 53 – LSM event rate/100 patient years	66.22	6.73	0.0052
Total 80 mg and 50 mg (≥2 events in 5 years Prior to enrollment): Adjudicated acute pancreatitis event rate from Week 1 to Week 53 – LSM event rate/100 patient years	118.59	16.59	0.0137

Source: Complete Study Report, Trial CS3
Abbreviations: LSM, least squares mean

Since the review team determined that the olezarsen 80 mg dose would be approved, it was decided (b) (4) the AP incidence for olezarsen 80 mg would be listed in the label. Specifically, the numerical incidence of AP in subjects treated with olezarsen 80 mg (n=1, 5%) was lower than placebo (n=7, 30%).

Conclusion

Yes, the secondary endpoint of reduction in the rate of AP is acceptable and clinically meaningful and therefore can be described in the olezarsen labeling.

Because of the failure of efficacy in TG reduction of olezarsen 50 mg dose (co-primary endpoint), all following endpoints, including AP did not meet statistical significance but were considered to be of nominal significance. However, the reduction in the AP rate with olezarsen 80 mg can be considered clinically significant. (b) (4)

(b) (4), future trials in sHTG populations, which are ongoing with olezarsen, may be able to provide additional effectiveness data.

6.3.4. Adequacy of the Confirmatory Evidence in Trial CS8 in the Severe and Moderate Hypertriglyceridemic Populations

Issue

Is Trial CS8, a phase 2 trial conducted in subjects with sHTG and mixed dyslipidemia, adequate to be used as confirmatory evidence for effectiveness of TG lowering in the FCS population?

Background

Requirements for Substantial Evidence of Effectiveness

Substantial evidence of effectiveness, the regulatory requirement for approval, generally consists of evidence from at least two adequate and well-controlled trials. In certain circumstances, a single adequate and well-controlled trial demonstrating efficacy may be sufficient to generate SEE if there is adequate confirmatory evidence. Such circumstances are described in the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023).

For example, clinical trial data from diseases with similarities in their underlying pathophysiology is appropriate for use as confirmatory evidence. Additionally, the degree of similarity between the efficacy endpoints in similar diseases can further support the use of these data as confirmatory evidence.

Other criteria for allowing use of confirmatory evidence includes the persuasiveness of the single investigation; the robustness of the confirmatory evidence; the seriousness of the disease, particularly when there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation.

These criteria and considerations are all relevant to the olezarsen development program for FCS, a very rare and serious disease with an unmet need. Because the olezarsen FCS program has only one adequate and well-controlled trial, we sought to assess whether there is adequate confirmatory evidence to generate SEE with Trial CS8, a phase 2 trial in severe and moderate HTG populations.

Causes and Classification of Hypertriglyceridemia

Plasma TG levels represent the TG content within various lipoprotein particles, mainly chylomicrons and VLDL. A fasting TG level below 150 mg/dL is generally considered within the normal range. Non-fasting TG levels of 175 mg/dL fall around the 75th percentile of the normal range, while levels of approximately 400 mg/dL are in the 97th percentile. In the general population, plasma TG levels are skewed to the right with a long tail toward higher values, varying based on population diversity. Due to this skew, a logarithmic transformation is used to define statistical normal ranges for TG levels, which can range from 30 mg/dL to 10,000 mg/dL. TG levels also differ between sexes, being higher in men than women, and they increase with age and the development of conditions like central adiposity, metabolic syndrome, and diabetes ([Subramanian 2000](#)).

FCS, sHTG and moderate HTG are all disorders characterized by elevated TG levels, but are differentiated by the degree of TG elevation, with moderate HTG populations generally characterized by TG between 150 mg/dL to 499 mg/dL, sHTG populations characterized by TG between 500 mg/dL to 1,000 mg/dL and FCS characterized by TG $\geq 1,000$ mg/dL. TG levels can overlap between categories; for example, some patients with sHTG can have TG over 1,000 mg/dL and patients with FCS with TGs in the range of sHTG.

HTG can be caused by various factors. Mild to moderate HTG is a complex and genetically diverse condition, typically polygenic, resulting from the combined effects of common and rare

variants in over 30 genes, as measured by genetic risk scores. All genetic forms can be worsened by environmental factors. Since these conditions arise from the interaction between multiple susceptibility genes and lifestyle factors such as poor diet, obesity, or diabetes, individuals with moderate to severe HTG should be treated as a single group, regardless of accompanying lipoprotein abnormalities. Due to the complexity of these disorders, routine genetic testing is not recommended ([Subramanian 2000](#)).

FCS is a rare genetic disorder characterized by extremely high TG levels, often above 2,000 mg/dL. The elevated TG in FCS are due to the accumulation of chylomicrons, large particles that carry TG from the intestines into the bloodstream. FCS results from mutations in genes involved in the breakdown of chylomicrons, most commonly the LPL gene, which impairs the body's ability to clear TG.

Both FCS and sHTG result from impaired TG metabolism. Both FCS and sHTG are associated with an increased risk of AP. Extremely high TG levels (>1,000 mg/dL) in both conditions can trigger this life-threatening inflammation of the pancreas. However, the risk is particularly high in FCS patients, who may experience recurrent pancreatitis even with modest elevations in TG levels.

Assessment

In Trial CS8, the primary efficacy endpoint of mean percent change in TG from baseline at Month 6 compared to placebo was met for both 80 mg olezarsen and 50 mg olezarsen treatment groups. Specifically, the placebo-adjusted mean percent change from baseline in TG was -56.5% for olezarsen 80 mg group (95% CI, -67.4, -45.6) and -51.7% (95% CI, -62.5, -41.0) for the olezarsen 50 mg group; p-value <0.0001 for both olezarsen treatment groups. Results of all sensitivity analyses on the mean percent change from baseline in fasting TG at Month 6 were consistent with the results for the primary efficacy endpoint.

In the 80 mg olezarsen treatment group, the mean baseline TG was 315 mg/dL (SD of 222 mg/dL) which decreased to 102 mg/dL (SD of 65 mg/dL) at Month 6. In the 50 mg olezarsen treatment group, the mean baseline TG was 292 mg/dL (SD of 183 mg/dL) which decreased to 115 mg/dL (SD of 76 mg/dL) at Month 6. In the placebo group, the mean baseline TG was 301 mg/dL (SD of 202 mg/dL) which decreased to 258 mg/dL (SD of 141 mg/dL) at Month 6.

The TG reduction with olezarsen treatment in Trial CS8 in the sHTG and moderate HTG population was consistent with the TG reduction in Trial CS3 in the FCS population. Not only were the results of Trial CS8 consistent, but the results were robust with a p-value of <0.0001. The TG reduction was also clinically meaningful with TG reductions that were below a threshold of 150 mg/dL, considered to be within normal range.

A sensitivity analysis using a non-parametric Wilcoxon rank sum test was conducted to explore the impact of distributional assumption on the analysis conclusion. The median percent change in TG from baseline to Month 6 endpoint was -68.6% for olezarsen 80 mg, and -15.0% for placebo. The median of the treatment difference between olezarsen 80 mg and placebo was -52.8% (95% CI -63.0, -42.6).

Another prespecified sensitivity analysis for the primary endpoint used a log transformation of TG data ([Table 39](#)). Testing was conducted to investigate whether the primary analysis was

sensitive to violation of the normality assumption. These sensitivity analyses were consistently in favor of olezarsen 80 mg over placebo.

Table 39. Sensitivity Analysis: Percent Change From Baseline in Fasting Triglycerides (mmol/L) at Month 6, ANCOVA Model Using Log-Transformed Data, Full Analysis Set, Trial CS8

Parameter	Olezarsen	Olezarsen	Placebo N=23
	50 mg N=21	80 mg N=22	
Month 6 log transformed Month 6 to baseline ratio			
LSM	-0.96	-1.10	-0.14
(95% CI)	(-1.07, -0.85)	(-1.21, -0.99)	(-0.27, 0.01)
% Change from baseline-100%*(back transformed Month 6 to baseline ratio - 1)			
LSM	-61.67	-66.56	-13.12
(95% CI)	(-65.64, -57.23)	(-70.04, -62.66)	(-23.96, -0.72)
Ratio of active to placebo in original scale			
LSM	0.44	0.39	
(95% CI)	(0.37, 0.52)	(0.32, 0.46)	
Nominal p-value	<.0001	<.0001	

Source: Clinical Study Report- Trial ID: ISIS 678354-CS8 Table 14.2.1.9, page 990

The primary analysis time point (Month 6) was defined as the average of Weeks 25 and 27.

Missing data after the last observed value for patients in the olezarsen arms were imputed using the J2R approach. Missing data before the last observed value or for patients in the placebo group were imputed under the MAR assumption. For each imputed data set, the percent change from baseline to Month 6 in fasting triglycerides (TG) between each Olezarsen treatment group (Olezarsen 80 mg, Olezarsen 50 mg) and placebo are compared using an ANCOVA model with $\log(y/x)$ as the dependent variable, where y is the value of TG at Month 6 and x is the baseline value of TG; treatment group is a factor; and the log-transformed baseline TG as a covariate. The model provides an estimate of log postbaseline to baseline ratio for each treatment group as well as the ratios relative to the Placebo group and the corresponding 95% confidence intervals (CIs).

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; J2R, Jump to Reference; LSM, least squares mean; N, total number of subjects; TG, triglycerides

In Trial CS8, there were no events of AP.

Conclusion

Yes, Trial CS8, a phase 2 trial conducted in subjects with severe and moderate HTG, is acceptable to be used as confirmatory evidence for effectiveness of TG lowering in the FCS population.

FCS and severe and moderate HTG are related through their shared impact on TG metabolism and their elevated risk for pancreatitis. However, while FCS is a rare genetic disorder caused by a single-gene defect, severe and moderate HTG are often a result of both genetic predisposition and environmental influences. Both conditions require careful management to prevent complications, especially pancreatitis.

6.3.5. Confirmation of Other Lipoproteins and Parameters in Trial CS3 in the FCS Population

Issue

Are the changes in LDL-C, total ApoB, non-HDL-C and ApoC-III in Trial CS3 confirmed by the statistical team?

Background

Understanding the changes in the overall lipid and lipoprotein profile is important because it can provide an assessment of the risk for CVD. Because Trial CS3 was of 53 weeks duration, and was not powered to evaluate cardiovascular risk reduction, the confirmation of lipid and lipoprotein changes was conducted to identify the changes that occurred during the trial. The lipid profile can guide healthcare providers to prescribe dietary changes, exercise, or medications (e.g., statins) to improve cholesterol levels as needed for the individual patient.

Elevated TG is a risk factor for AP. Additionally, elevated TG and LDL-C are both risk factors for CVD. TG are mainly transported by VLDL. As VLDL particles release TG into tissues (via lipoprotein lipase), they become smaller, denser particles called LDL, which are richer in cholesterol. Therefore, when TG are removed from the bloodstream, the number of LDL particles can increase, raising LDL-C levels ([Feingold 2022](#)).

ApoC-III plays several important roles in lipid metabolism, particularly in the regulation of TG levels. Its main functions include inhibition of lipoprotein lipase, an enzyme responsible for breaking down TG contained within VLDL-C and chylomicrons. By inhibiting LPL, ApoC-III slows the breakdown and clearance of TG from the bloodstream. ApoC-III also impairs the liver's ability to remove TG rich lipoproteins from circulation by inhibiting their uptake by hepatic receptors. For these reasons, ApoC-III has is a target for therapies aimed at reducing TG, such as olezarsen.

Assessment

Refer to Section [6.2.2.6](#) to review changes in LDL-C, non-HDL-C, total ApoB, and ApoC-III. Refer also to Section [16](#) for additional lipid analyses (waterfall plots). In Trial CS3, mean LDL-C increased, mean non-HDL-C decreased, and there were slight increases in mean total ApoB with olezarsen 80 mg as compared to placebo. ApoC-III levels were also decreased with olezarsen treatment versus placebo.

The observed increases in LDL-C are consistent with the effects of other TG-lowering medications in patients with sHTG. The mean LDL-C values remained below 100 mg/dL for olezarsen 80 mg/dL. On average, non-HDL-C levels decreased with olezarsen treatment, although total ApoB increased slightly compared to placebo. The net effect on atherosclerotic risk is unknown. One (1.8%) and three (5.2%) patients in the olezarsen 80 mg and 50 mg groups, respectively, experienced MACE treatment-emergent adverse events (TEAEs) during the study, while no patients in the placebo group experienced such an event. MACE events are discussed further in Section [7](#).

Non-HDL-C includes all forms of atherogenic cholesterol such as LDL-C, VLDL-C, and intermediate-density lipoprotein. Non-HDL-C may be a more accurate predictor of CVD risk than LDL-C alone, especially in people with moderately high TG or metabolic disorders. In the FCS population, non-HDL-C levels decreased with olezarsen 80 mg to a greater degree than placebo. The clinical significance of the change in non-HDL-C in the FCS population is unknown.

Total ApoB is a measure of the total number of atherogenic lipoproteins in the blood. ApoB is a protein found on the surface of certain lipoproteins, including LDL-C, VLDL-C, intermediate-

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density lipoprotein and lipoprotein(a). The increase in total ApoB may reflect the increase in LDL-C seen with olezarsen treatment.

ApoC-III slows down the clearance of TG from the blood and inhibits the action of LPL, leading to HTG. ApoC-III levels were decreased with olezarsen treatment confirming the mechanism of action of olezarsen.

Conclusion

Yes, the lipid parameters LDL-C, non-HDL-C, total ApoB and ApoC-III levels were confirmed by the statistical team. These changes in the lipid profile (LDL-C, non-HDL-C, and total ApoB) are expected based on the lipid metabolism pathway and do not alter the favorable benefit-risk profile of olezarsen 80 mg of reducing TG and the risk of AP. The reduction of ApoC-III confirmed the mechanism of action of olezarsen. The results of these lipid and lipoprotein parameters will be shown in the olezarsen label.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical evaluation of the safety of olezarsen included repeat-dose general toxicology studies of up to 26 and 39-weeks in duration with 13 and 26-week recovery periods in mice and monkeys, respectively, an evaluation of effects on male and female fertility and early embryonic development in mice, a battery of genotoxicity studies in vitro (bacterial reverse mutation assay and chromosomal aberration assay) and in vivo (micronucleus assay in mouse), and an impurity qualification toxicity study. Carcinogenicity, embryofetal development, and pre-/postnatal development toxicity studies were not scientifically justified for olezarsen because studies conducted with the unconjugated active ASO (volanesorsen) provided acceptable assessments of carcinogenic, embryo-fetal development, and pre-/postnatal risk.

Potentially clinically relevant observations from repeat-dose toxicity studies with olezarsen (also observed with volanesorsen, the unconjugated ASO) included thrombocytopenia, effects on the liver, injection site reactions, and hypersensitivity/inflammatory responses, which are summarized below.

Thrombocytopenia

Reductions in platelet counts were noted in mice and monkeys following SC administration of olezarsen, which was anticipated based on similar findings with volanesorsen. In a 13-week mouse toxicity study that included a 13-week recovery period, a 25% reduction in platelet count was reported in females administered 24 mg/kg/wk olezarsen (~6x maximum recommended human dose based on body surface area [BSA]) that was reversible. However, reductions in platelet counts were not observed in the 26-week mouse study at doses up to 20 mg/kg/wk (~5x MRHD_{BSA}).

In a 39-week monkey toxicity study that included a 26-week recovery period, olezarsen induced a marked reduction in platelet count (>98% decrease) in a single male animal at the 12 mg/kg/wk

dose (12x MRHD_{BSA}) on Day 65, resulting in petechia and oral mucosal bleeding. The platelet count recovered following treatment with methylprednisolone but was again reduced (~95%) at the scheduled termination of this animal at Week 13.

These findings were considered treatment-related and adverse considering prior observations of thrombocytopenia with volanesorsen in both mice and monkeys at clinically relevant doses. Thrombocytopenia and bleeding events were monitored during clinical development (Section [7.2](#))

Hepatic Findings

Drug-related histopathology findings were reported in the liver of both mice and monkeys following SC administration of olezarsen. In the 26-week mouse toxicity study with olezarsen, dose-related increases in the incidence and severity of hepatocellular hypertrophy, cytoplasmic alteration, karyomegaly, increased mitotic figures, and vacuolated/granular macrophages were noted. These microscopic findings correlated with increased absolute (by up to ~60%) and relative liver weights at ≥ 6 mg/kg/wk (~1.5x MRHD_{BSA}) and increases in liver enzymes (approximately 3-fold AST, 7-fold ALT and 2-fold alkaline phosphatase) at 20 mg/kg/wk dose (~5x MRHD_{BSA}) in both sexes compared to control. These effects were reversible.

Hepatic-related events were also observed in a 39-week monkey toxicity study with olezarsen. Liver findings included increases (over baseline) in ALT (4-fold increase), AST (1.6-fold increase) and glutamate dehydrogenase (~5-fold) at ≥ 6 mg/kg/wk (~6x MRHD_{BSA}). The increases in liver enzymes correlated with microscopic observations of basophilic granules in hepatocytes and Kupffer cells (along with Kupffer cell hypertrophy). At ≥ 12 mg/kg/wk (~12x MRHD_{BSA}), increases (up to 2-fold) in absolute and relative liver weights occurred. The effects on liver enzymes and liver weight were reversible.

From a nonclinical perspective, the liver is considered a target organ but with uncertain translatability to humans. These observations in animals are known to be associated with ASO uptake and accumulation in the liver, leading to hepatocellular vacuolation, hepatocellular single-cell necrosis, and Kupffer cell hypertrophy resulting from the presence of basophilic granules in the liver of both mouse and monkey ([Frazier 2015](#)). Vacuolated or granular macrophages in the liver are also associated with cellular activation and cytokine production by the proinflammatory properties of ASOs ([Engelhardt et al. 2015](#)). These effects were associated with liver weight increases and with increases in liver enzymes. The effects on the liver were generally reversible as the incidence/severity was lessened following a recovery period. Humans are thought to be less sensitive to these effects, but liver safety was carefully monitored during clinical development (Section [7.2](#)).

Injection Site Reactions

Injection site reactions were observed in the 26-week mouse and 39-week monkey toxicity studies. In mice, vacuolated/granular macrophages were observed in the skin and injection sites at all dose levels (≥ 2 mg/kg/wk, ~0.5x MRHD_{BSA}). Mononuclear cell infiltration and basophilic granules in histiocytes were also found in both sexes at the injection site. In monkeys, minimal to marked mononuclear cell infiltration or slight acute inflammation was observed at the injection sites at ≥ 6 mg/kg/wk (~6x MRHD_{BSA}). These microscopic changes are consistent with the pro-

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inflammatory effects seen in animals with ASOs. Injection-site reactions were monitored during clinical development (Section [7.2](#)).

Hypersensitivity/Inflammatory Reactions

Changes in biomarkers indicative of hypersensitivity reactions were observed in the mouse and monkey toxicity studies.

In the 26-week mouse study, an increase in the potent inflammatory cytokine, monocyte chemoattractant protein-1, which suggests an inflammatory response. In addition, IgM decreased in males at $\geq$ mid dose (up to 40% lower) and in females at $\geq$ low dose (up to 58%). This effect was reversible in the 13-week recovery group. In the 39-week monkey study, complement activation was observed. Dose-dependent increases in complement Bb were seen at all dosages. Up to 3-fold (females) and up to 21-fold (males) at 12 and 30 mg/kg/wk and up to 3.6-fold (males) and 5.5-fold (females) at ≥ 2 mg/kg/wk. Increases in complement Bb was accompanied by decreases in complement C3 at all dosages in males and at 12 and 30 mg/kg/wk in females. Effects indicative of generalized inflammation occurred primarily at dosages >12 mg/kg and included increases in C-reactive peptide, monocyte chemoattractant protein-1 (MCP-1), and/or gamma interferon (IFN γ) levels.

Phosphorothioate oligonucleotides are reported to cause the release cytokines in rodents and nonhuman primates secondary to complement activation ([Henry et al. 2002](#)), but humans are generally considered less sensitive than these animal models. Monkeys are generally more sensitive to 2'-O-methoxyethyl (2' MOE) ASO-mediated complement activation than humans ([Shen et al. 2014](#)). Monitoring for hypersensitivity reactions was conducted during clinical development.

Mutagenicity/Carcinogenicity

Olezarsen was not mutagenic in vitro or in vivo. Carcinogenicity studies were not conducted with olezarsen, but lifetime carcinogenicity studies were conducted for the active unconjugated ASO, volanesorsen, in both mice and rats. These carcinogenicity studies identified increased incidences of neoplasms in both mice and rats. Increases in hepatocellular adenomas and carcinomas, hemangiomas and hemangiosarcomas, histiocytic sarcomas, and pituitary gland adenomas were observed in mice, while malignant fibrous histiocytomas at the injection site were observed in rats. These findings are likely related to the increased sensitivity of rodents to the proinflammatory effects of phosphorothioate oligonucleotides and/or the method of administration and have also been reported in carcinogenicity studies with other ASOs. Therefore, the clinical relevance of these tumors is uncertain but may be limited.

Reproductive Safety

No significant risk for pregnancy or embryo-fetal development was detected in studies with volanesorsen in mice and rats. Refer to Section [8.4](#) of this review for labeling recommendations.

Conclusion

Overall, administration of olezarsen in animals at clinically relevant exposures was well-tolerated. Observations identified with olezarsen in the 26-week mouse and 39-week monkey studies of potential clinical relevance were thrombocytopenia, effects in liver, injection site

reactions, and hypersensitivity/inflammatory responses. Most of the effects are consistent with those reported for other ASOs, and indeed some of these effects were also noted clinically (see Section 7.7). The clinical significance of the changes in complement activation observed in cynomolgus monkeys is unclear, but monkeys are generally thought to have increased sensitivity compared to humans. The safety margins and multiples for these observations from these pivotal studies are summarized below in Table 40.

Table 40. Clinically Relevant Nonclinical Observations and Safety Margins

Study (Doses)	NOAEL ¹ (mg/kg/wk)	Nonclinical Exposure (AUC _{0-48hr}) (µg*h/mL)	BSA (mg/m ²)	Safety Margins ²	Basis for NOAEL
26-week mouse (0, 2, 6, 20 mg/kg/wk by s.c.) ³	2	NA	24	≤1x	- Dose-related increased absolute and relative liver weights (up to 60%) at ≥6 mg/kg/wk (~1.5x MRHD_{BSA}) in both sexes correlated with hepatocellular hypertrophy, cytoplasmic alteration, karyomegaly, increased mitotic figures and vacuolated/granular macrophages - Increases in liver enzymes (up to 7-fold) at 20 mg/kg/wk (5x MRHD_{BSA})
39-week monkey (0, 2, 6, 12 mg/kg/wk by s.c.)	6	141	288	6x	Significant decrease in platelet count in one male monkey at 12 mg/kg (~12x MRHD_{BSA})

Source: Reviewer-generated table.

¹ Converting NOAEL in animals from mg/kg/wk to mg/kg/month, multiply by 4. BSA is based on the monthly dose.

² Human dose = 80 mg/month, equivalent to 1.33 mg/kg/month for a 60-kg adult, equivalent to 49 mg/m² based on BSA. Safety margins were based on BSA for an 80 mg maximum recommended human dose.

³ The mouse specific ASO ISIS 838707 was also evaluated at 6 mg/kg/wk in this study

Abbreviation: AUC, area under the concentration-time curve; BSA, body surface area; MRHD, maximum recommended human dose; NA, not available; NOAEL, no observed adverse effect level; s.c., subcutaneous injection

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns for olezarsen were initially based on the clinical experiences with volanesorsen and information known about anti-sense oligonucleotides in general. The safety profile of volanesorsen and/or antisense oligonucleotides is characterized by hypersensitivity reactions/flu-like reactions (Section 7.7.1), injection site reactions (Section 7.7.5), thrombocytopenia and bleeding events (Section 7.7.2), hepatic-related events (Section 7.7.3), dysglycemia (Section 7.7.4), changes in LDL-C and ApoB (Section 7.7.6), and immunogenicity (Section 7.7.8). These topics informed the key safety review issues. For further discussion of these issues, refer to the relevant sections hyperlinked above.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Adverse Events Identified in Postmarket Experiences

Although olezarsen is not yet commercially available in any country, volanesorsen shares the same identical oligonucleotide sequence as olezarsen and is approved outside of the United States. Given their similarities, the Applicant was asked to provide a summary of safety for volanesorsen based on the global experience of volanesorsen exposure. Volanesorsen was granted conditional marketing approval in the European Economic Area member states in 2019 and in Great Britain in 2021. Marketing authorization was received in Brazil in 2021, (b) (4). Volanesorsen is indicated in all of these countries as an adjunct to diet in adult patients with FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

As of November 2, 2023, the estimated cumulative postmarketing exposure is 226.6 patient years and (b) (4) individuals have been exposed to commercial volanesorsen. The important identified and potential risk are thrombocytopenia, injection site reactions, immunogenicity, hepatotoxicity, and nephrotoxicity. There have been no new safety signals identified for volanesorsen in the postmarket setting. A search of medical literature using PubMed and the search term ‘volanesorsen’, did not yield reports of new safety findings.

7.3.2. Expectations on Safety

It is anticipated that olezarsen’s safety profile in the postmarket setting, when used in the indicated treatment population, will be similar to the safety experience in the clinical trial population. (b) (4)

Given that this application seeks a treatment indication in a rare disease population, one would expect the number of subjects exposed to olezarsen in the postmarket setting to be small. A higher-than-expected amount of olezarsen patient exposure could suggest off-label treatment in other HTG populations. Because the clinical trials of olezarsen in other HTG populations are blinded and ongoing, the benefits and risks in an off-label population are unknown.

7.3.3. Additional Safety Issues From Other Disciplines

None.

7.4. FDA Approach to the Safety Review

Clinical study data were analyzed using JMP and JMP Clinical software. Clinical data scientists (CDSs) from the Division of Biomedical Informatics generated the safety tables and figures,

unless otherwise noted. These include safety tables and figures for patient disposition, exposure data, AEs, and serious adverse events (SAEs).

Phase 1 and 2 trials were screened for safety signals that may not have been identified in the phase 3 program.

The safety population in all clinical trials was defined as randomized subjects who received at least one dose of study drug. Subjects were analyzed in the treatment group according to the actual treatment they received.

The primary data for review of olezarsen safety was from CS3, the pivotal, 53-week, placebo-controlled trial in adults with FCS. Supportive safety data was provided in CS8, the 53-week placebo-controlled trial in adults with moderately elevated TG at risk for ASCVD and adults with high TG. Two open-label trials in adults with FCS, CS13 and CS7, provide additional supportive safety data. All eligible subjects completing treatment in CS3 could elect to enroll in an OLE study, CS13, and Trial CS7 provides safety information from adults with FCS that had been previously treated with volanesorsen.

The Applicant provided several pooled analyses using different combinations of the above trials including a pool of the phase 3 placebo-controlled trials, CS3 and CS8, a pool of studies of individuals with FCS – CS3, CS7, CS13, and a pool of all phase 2/3 trials – CS2, CS3, CS8, CS7, and CS13. Although the phase 3 trial designs share a placebo-controlled period and dosing regimen of olezarsen, both trials had key differences that may impact the types and frequency of events, including different patient populations and treatment allocation (1:1 vs. 2:1). Open-label trials have inherent biases given treatment assignment is known which may impact both trial participants and individuals involved in the study conduct. Therefore, pooling an open-label trial with a placebo-controlled blinded trial may be limited in its ability to interpret a drug's true effect. For this safety review, longitudinal data on subjects participating in CS3 and CS13 was evaluated such as platelet count changes over time. However, in general, in this clinical reviewer's opinion, pooling did not provide additional information that cannot be gleaned from review of the individual trial safety data. Therefore, this review does not present pooled safety data.

In Trials CS3 and CS8, a TEAE was defined as an event present prior to receiving the first dose of study drug and subsequently worsens, or it was not present prior to receiving the first dose of study drug but subsequently appeared.

SAEs were defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization or prolonged a current hospitalization, cause persistent or significant disability/incapacity, or was a congenital anomaly/birth defect in the offspring of a subject who received study drug. In addition, any event that required intervention to prevent one of these outcomes could be considered a serious adverse event (SAE) (i.e., allergic bronchospasm requiring intensive treatment in an emergency department or home), but this was at the judgment of the investigator.

Following discussion between the clinical reviewers and clinical data scientist teams, the following were implemented in the safety analyses, first because adjudicated pancreatitis events were considered clinical endpoints of efficacy, these events were excluded from the safety tables and figures. Second, the Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in the trial. The

translations were reviewed, and several verbatim terms noted events occurring during or shortly after administration of study drug which were recoded with the preferred term ‘injection related reaction’. For example, a verbatim term ‘IP INJECTION REACTION DIARRHEA (sp) AFTER 15 MINUTES’ was coded by the Applicant with the preferred term of ‘Diarrhoea’. This event was considered more consistent with a hypersensitivity reaction and was recoded as ‘injection related reaction’ by the review team.

7.5. Adequacy of the Clinical Safety Database

The safety database for this application is small, due in part to the rarity of the FCS population. The Applicant was strongly encouraged, before phase 3 was initiated, to bolster the safety database by increasing the size of studies investigating olezarsen in other patient populations, especially since the Applicant was contemplating development of olezarsen for the more common severe hypertriglyceridemia population (i.e., non-FCS, TG $\geq$ 500 mg/dL) at the time. In response, the Applicant conducted a small (n=154), 53-week, placebo-controlled trial (CS8) in patients with moderate HTG with or at risk for ASCVD and patients with sHTG.

Limitations of this safety database include differences in the CS3 and CS8 populations in regard to comorbidities, concomitant medications, and treatment objectives (i.e., the majority of subjects in CS8 had moderate HTG with risk for ASCVD and therefore the primary objective is to reduce the frequency of MACE versus pancreatitis). These factors may limit the generalizability of the safety findings in Trial CS8 to the FCS population. Another gap in the safety database is the absence of safety data available to evaluate the effect of olezarsen in pediatric patients with FCS, a condition that presents during childhood. The Applicant has an agreed Pediatric Investigation Plan with the European Medicine Agency that is deferred ^{(b) (4)} to determine pediatric dosing (EMA 2023). Therefore, it is possible, especially given the size of the database, that additional safety signals may emerge or be more clearly characterized with additional exposure in patients with FCS.

However, the strengths of the safety database include the placebo-controlled design, use of two doses to assess dose-response, and the 1-year treatment duration in this rare disease population, with additional longer-term exposure in the OLE. In addition, there were very few study drop-outs and the amount of missing data is small. Trial CS8, despite its limitations provides additional supportive safety information from a placebo-controlled trial in an HTG population.

Overall, the safety database is adequate to assess the safety of olezarsen for the proposed indication, dosage regimen, and patient population.

At the time of the various data-cutoffs, a total of 202 subjects were exposed to olezarsen in the phase 2/3 program, including 87 subjects with FCS. Of these 87 subjects, 54 had at least 12 months exposure to olezarsen (35 subjects at 80 mg and 19 subjects at 50 mg or 80 mg). Table 41 below provides the number of subjects exposed to either olezarsen or placebo in the phase 2/3 program. Treatment exposure for Trials CS3 and CS8 follow the table.

Table 41. Number of Subjects Exposed in Phase 2/3 Program

Clinical Trial Initial Data Cutoff	Olezarsen		Placebo
	50 mg	80 mg	
CS3-pivotal 14 July 2023	21	22	23

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Clinical Trial Initial Data Cutoff	Olezarsen		Placebo
	50 mg	80 mg	
CS8-HTG 15 September 2023	58	57	39
CS13-OLE 5 August 2023	NA	20 (treatment-naïve)	NA
CS7-OL 31 May 2023	NA	24	NA

Source: Safety clinical reviewer generated table, table does not include trial CS2, which did not study the 80 mg olezarsen dose
Abbreviations: HTG, hypertriglyceridemia; OL, open-label; OLE, open-label extension

A summary of the exposures in Trials CS3 and CS8 are shown in [Table 42](#) and [Table 43](#) below.

Table 42. Duration of Exposure, Safety Population, Trial CS3

Parameter	Olezarsen 50 mg N=21	Olezarsen 80 mg N=22	Placebo N=23
Duration of treatment, days			
Mean (SD)	339.3 (84.6)	323.4 (107.7)	353.1 (35.9)
Median (Q1, Q3)	365 (363, 365)	364 (364, 366)	364 (362.5, 364)
Min, max	57, 388	28, 400	199, 368
Total exposure (person years)	20	19	22
Patients treated, by duration, n (%)			
1 to 89 days	1 (4.8)	2 (9.1)	0 (0)
90 to 179 days	1 (4.8)	1 (4.5)	0 (0)
180 to 359 days	0 (0)	1 (4.5)	4 (17.4)
360 to 400 days	19 (90.5)	18 (81.8)	19 (82.6)
>400 days	0	0	0
Number of injections, n (%)			
Mean (SD)	11.7 (3)	11 (3.8)	12.1 (1.9)
Median (min, max)	13 (2, 13)	13 (1, 13)	13 (6, 13)
1 injection	0 (0)	2 (9.1)	0 (0)
>1 to ≤7 injections	2 (9.5)	1 (4.5)	2 (8.7)
>7 to ≤13 injections	19 (90.5)	19 (86.4)	21 (91.3)
>13 injections	0	0	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is up to 400 days.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 43. Duration of Exposure, Safety Population, Trial CS8

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Placebo N=39
Duration of treatment, days			
Mean (SD)	311.9 (100.9)	335.6 (77.8)	351.2 (45.6)
Median (Q1, Q3)	364 (361, 365)	364 (361, 365)	364 (362, 365)
Min, max	56, 371	84, 374	168, 369
Total exposure (person years)	50	52	38

Parameter	Olezarsen 50 mg N=58	Olezarsen 80 mg N=57	Placebo N=39
Patients treated, by duration, n (%)			
1 to 89 days	4 (6.9)	1 (1.8)	0 (0)
90 to 179 days	6 (10.3)	5 (8.8)	1 (2.6)
180 to 359 days	4 (6.9)	2 (3.5)	2 (5.1)
360 to 400 days	44 (75.9)	49 (86.0)	36 (92.3)
>400 days	0	0	0
Number of injections, n (%)			
Mean (SD)	10.8 (3.7)	11.6 (2.8)	12.3 (1.7)
Median (min, max)	13 (2, 13)	13 (3, 13)	13 (6, 13)
>1 to ≤7 injections	13 (22.4)	7 (12.3)	3 (7.7)
>7 to ≤13 injections	45 (77.6)	50 (87.7)	36 (92.3)

Source: adex.xpt and adsl.xpt; Software: R

Duration is up to 374 days.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Trials ISIS 678354-CS3 and ISIS 678354-CS8

Not applicable. See Section [7.4](#) for the approach to safety review.

7.6.2. Safety Results, Trial ISIS 678354-CS3

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial CS3

[Table 44](#) provides an overview of the TEAEs, excluding adjudicated pancreatitis events. Most subjects reported an AE, however a lower proportion of subjects treated with olezarsen had a TEAE or SAE. A higher number of olezarsen-treated subjects experienced an AE that led to permanent discontinuation of study drug; however, these numbers were low – one subject in the olezarsen 50 mg group, and two subjects in the olezarsen 80 mg group.

Table 44. Overview of Adverse Events, Safety Population, Trial CS3

Event Category	Olezarsen 50 mg N=21 n (%)	Olezarsen 80 mg N=22 n (%)	Placebo N=23 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
SAE	3 (14.3)	2 (9.1)	6 (26.1)	-11.8 (-35.5, 13.3)	-17.0 (-39.6, 6.3)
SAEs with fatal outcome	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Life-threatening SAEs	0	0	0	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
AE leading to permanent discontinuation of study drug	1 (4.8)	2 (9.1)	0	4.8 (-10.2, 23.0)	9.1 (-6.2, 28.1)
AE leading to dose modification of study drug	1 (4.8)	4 (18.2)	2 (8.7)	-3.9 (-23.2, 15.6)	9.5 (-12.1, 31.8)
AE leading to interruption of study drug	1 (4.8)	3 (13.6)	2 (8.7)	-3.9 (-23.2, 15.6)	4.9 (-15.8, 26.5)
AE leading to reduction of study drug	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
AE leading to dose delay of study drug	0	0	0	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Any AE	18 (85.7)	19 (86.4)	21 (91.3)	-5.6 (-27.8, 15.4)	-4.9 (-26.5, 15.8)
Severe and worse	3 (14.3)	0	6 (26.1)	-11.8 (-35.5, 13.3)	-26.1 (-46.7, -9.1)*
Moderate	6 (28.6)	9 (40.9)	8 (34.8)	-6.2 (-32.8, 21.6)	6.1 (-21.9, 33.4)
Mild	9 (42.9)	10 (45.5)	7 (30.4)	12.4 (-16.1, 39.4)	15.0 (-13.5, 41.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as any AE events starting or getting worse on or after the first dose of the study drug.

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Severity as assessed by the investigator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, Trial CS3

There was one death in the olezarsen 50 mg group in Trial CS3. A summary is included here.

- Subject #CS3-(b) (6); CS3 – Sudden death (unknown cause), olezarsen 50 mg Q4W – 74-year-old female with a medical history of pancreatitis and hypertension. The patient was receiving the concomitant medications calcifediol, calcium carbonate, cholecalciferol, denosumab, gemfibrozil, hydrochlorothiazide, losartan, manidipine, and omeprazole. She had been previously treated with volanesorsen in Trial CS7 OLE study for 1.5 years. She discontinued volanesorsen due to a nonserious treatment-emergent adverse event (TEAE) of polymyalgia rheumatica and had been off volanesorsen for 2.5 years. The subject had received two doses of olezarsen 50 mg prior to her death. The subject died suddenly while she was making dinner on Study Day 42 (12 days post last dose of olezarsen). There were no symptoms in the minutes or hours prior to the event. No TEAEs, clinically meaningful laboratory results, or electrocardiogram (ECG) abnormalities were reported for the patient prior to the death. The cause of death remains unknown. No autopsy details or death certificate were available.

Following review of the narratives and case report forms, it is difficult to discern olezarsen's contribution, if any, to this death given the limited information available.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial CS3

Narratives, as well as relevant datasets, and case report forms were reviewed for these events. These events are further described, where applicable, in the key safety review topics (i.e., serious hepatic-related event of cirrhosis is discussed in Section [7.7.3](#))

The number and percentage of subjects with a treatment-emergent SAE were lower in the olezarsen-treatment groups. A review of the SAEs did not yield a safety signal for olezarsen due to the low number of events and alternative causative etiologies (e.g., SAE of intestinal perforation secondary to a foreign body ingestion; SAE of bacterial gastroenteritis confounded by recent travel history; SAE of intentional overdose confounded by concurrent medical history of post-traumatic stress disorder treated with antidepressant medication).

Table 45. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CS3

System Organ Class Preferred Term	Olezarsen 50 mg N=21 n (%)	Olezarsen 80 mg N=22 n (%)	Placebo N=23 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Any SAE	3 (14.3)	2 (9.1)	6 (26.1)	-11.8 (-35.5, 13.3)	-17.0 (-39.6, 6.3)
Gastrointestinal disorders (SOC)	0	1 (4.5)	3 (13.0)	-13.0 (-32.4, 3.7)	-8.5 (-28.7, 11.0)
Intestinal perforation	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Gastric varices	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Gastric varices haemorrhage	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Gastritis	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Pancreatitis	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
General disorders and administration site conditions (SOC)	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Sudden death	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Hepatobiliary disorders (SOC)	0	1 (4.5)	1 (4.3)	-4.3 (-21.3, 11.8)	0.2 (-17.4, 18.4)
Hepatic cirrhosis	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Cholangitis	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Infections and infestations (SOC)	1 (4.8)	0	1 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Gastroenteritis bacterial	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Cellulitis	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Injury, poisoning and procedural complications (SOC)	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Intentional overdose	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Metabolism and nutrition disorders (SOC)	0	0	2 (8.7)	-8.7 (-27.1, 7.8)	-8.7 (-27.1, 7.1)
Hypoglycaemia	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Hyponatraemia	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Pancreatogenous diabetes	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Squamous cell carcinoma of the oral cavity	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as any AE events starting or getting worse on or after the first dose of the study drug.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, Trial CS3

Results of the FDA analysis of AEs leading to treatment discontinuation (DAE) for Trial CS3 are shown in [Table 46](#). Overall, there were very few subjects (one subject olezarsen 50 mg – ‘sudden death’ described in Section 7.6.2.2; two subjects olezarsen 80 mg) that discontinued due to an AE. The two subjects (CS3-^{(b) (6)}; CS3-^{(b) (6)}) treated with 80 mg olezarsen discontinued treatment due to a hypersensitivity or flu-like reaction. This key safety review issue is further described in Section 7.7.1. FMQ analysis was done but did not yield additional information.

Table 46. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CS3

System Organ Class Preferred Term	Olezarsen	Olezarsen	Placebo N=23 n (%)	Olezarsen	Olezarsen
	50 mg N=21 n (%)	80 mg N=22 n (%)		50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Any AE leading to discontinuation	1 (4.8)	2 (9.1)	0	4.8 (-10.2, 23.0)	9.1 (-6.2, 28.1)
Gastrointestinal disorders (SOC)	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Diarrhoea	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Vomiting	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
General disorders and administration site conditions (SOC)	1 (4.8)	2 (9.1)	0	4.8 (-10.2, 23.0)	9.1 (-6.2, 28.1)
Chest discomfort	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Chills	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Sudden death	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Myalgia	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Trismus	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Vascular disorders (SOC)	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Flushing	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as any AE events starting or getting worse on or after the first dose of the study drug.

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Trial CS3

Results of the FDA analysis of TEAEs by preferred term and by FMQ that occurred in $\geq 5\%$ of subjects in any treatment arm for CS3 are shown in [Table 47](#) and [Table 48](#). A higher proportion of subjects in the placebo group compared to the olezarsen treatment groups reported a TEAE. FMQs that had a larger risk difference in the 80 mg olezarsen treatment groups versus placebo were related to reductions in platelet count, injection site reactions, nasopharyngitis, anemia,

vomiting, dyspnea, arthralgia, urinary tract infections. Discussion of the key safety review topics regarding reduction in platelet count, injection site reactions, are discussed in Sections 7.7.

It was noted that the preferred term ‘anxiety’ occurred in three (14.3%) subjects and the FMQ anxiety occurred in four (19%) subjects treated with olezarsen 50 mg and none in either the olezarsen 80 mg or placebo treatment groups. Review of the anxiety AEs at subject level did not suggest a relatedness to study drug. There was also no imbalance for anxiety or other psychiatric FMQs for olezarsen 80 mg. Note that the FMQ ‘Study agent abuse potential’ is populated by the preferred term, ‘somnolence’ in the 80 mg olezarsen group, which on its own does not suggest a safety signal for potential abuse.

Table 47. Patients With Common Adverse Events Occurring at ≥5% Frequency, Safety Population, Trial CS3

Preferred Term	Olezarsen	Olezarsen	Placebo N=23 n (%)	Olezarsen	Olezarsen
	50 mg N=21 n (%)	80 mg N=22 n (%)		50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Any AE	18 (85.7)	19 (86.4)	21 (91.3)	-5.6 (-27.8, 15.4)	-4.9 (-26.5, 15.8)
Pain in extremity	2 (9.5)	3 (13.6)	1 (4.3)	5.2 (-13.3, 25.6)	9.3 (-9.7, 30.1)
Platelet count decreased	1 (4.8)	3 (13.6)	1 (4.3)	0.4 (-17.2, 19.3)	9.3 (-9.7, 30.1)
Abdominal distension	0	2 (9.1)	0	0.0 (-14.6, 15.8)	9.1 (-6.2, 28.1)
Vomiting	1 (4.8)	2 (9.1)	0	4.8 (-10.2, 23.0)	9.1 (-6.2, 28.1)
Abdominal pain upper	2 (9.5)	2 (9.1)	1 (4.3)	5.2 (-13.3, 25.6)	4.7 (-13.6, 24.5)
Anaemia	0	2 (9.1)	1 (4.3)	-4.3 (-21.3, 11.8)	4.7 (-13.6, 24.5)
Injection site erythema	1 (4.8)	2 (9.1)	1 (4.3)	0.4 (-17.2, 19.3)	4.7 (-13.6, 24.5)
Arthralgia	3 (14.3)	1 (4.5)	0	14.3 (-1.4, 34.9)	4.5 (-10.4, 22.1)
Injection site pain	2 (9.5)	1 (4.5)	0	9.5 (-5.8, 29.2)	4.5 (-10.4, 22.1)
Urinary tract infection	3 (14.3)	1 (4.5)	0	14.3 (-1.4, 34.9)	4.5 (-10.4, 22.1)
Cough	2 (9.5)	2 (9.1)	2 (8.7)	0.8 (-19.3, 22.0)	0.4 (-19.6, 20.9)
Nasopharyngitis	2 (9.5)	1 (4.5)	1 (4.3)	5.2 (-13.3, 25.6)	0.2 (-17.4, 18.4)
Nausea	2 (9.5)	1 (4.5)	1 (4.3)	5.2 (-13.3, 25.6)	0.2 (-17.4, 18.4)
Anxiety	3 (14.3)	0	0	14.3 (-1.4, 34.9)	0.0 (-14.6, 15.2)
Arthropod bite	2 (9.5)	0	0	9.5 (-5.8, 29.2)	0.0 (-14.6, 15.2)
Upper respiratory tract infection	2 (9.5)	0	0	9.5 (-5.8, 29.2)	0.0 (-14.6, 15.2)
Back pain	0	1 (4.5)	2 (8.7)	-8.7 (-27.1, 7.8)	-4.2 (-23.3, 14.7)
Hypoglycaemia	1 (4.8)	1 (4.5)	2 (8.7)	-3.9 (-23.2, 15.6)	-4.2 (-23.3, 14.7)
Influenza	3 (14.3)	1 (4.5)	2 (8.7)	5.6 (-15.4, 27.8)	-4.2 (-23.3, 14.7)
Skin laceration	1 (4.8)	1 (4.5)	2 (8.7)	-3.9 (-23.2, 15.6)	-4.2 (-23.3, 14.7)
Epistaxis	2 (9.5)	0	1 (4.3)	5.2 (-13.3, 25.6)	-4.3 (-21.3, 11.1)
Headache	4 (19.0)	1 (4.5)	3 (13.0)	6.0 (-17.0, 29.7)	-8.5 (-28.7, 11.0)
Dental caries	0	0	2 (8.7)	-8.7 (-27.1, 7.8)	-8.7 (-27.1, 7.1)
Gastroesophageal reflux disease	0	0	2 (8.7)	-8.7 (-27.1, 7.8)	-8.7 (-27.1, 7.1)
Hyponatraemia	0	0	2 (8.7)	-8.7 (-27.1, 7.8)	-8.7 (-27.1, 7.1)
Migraine	1 (4.8)	0	2 (8.7)	-3.9 (-23.2, 15.6)	-8.7 (-27.1, 7.1)
Proteinuria	0	0	2 (8.7)	-8.7 (-27.1, 7.8)	-8.7 (-27.1, 7.1)
Fatigue	1 (4.8)	1 (4.5)	4 (17.4)	-12.6 (-33.6, 8.1)	-12.8 (-33.8, 7.3)

NDA 218614
Tryngolza (olezarsen sodium)

Preferred Term	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs.	80 mg vs.
	N=21	N=22	N=23	Placebo	Placebo
	n (%)	n (%)	n (%)	Risk Difference	Risk Difference
				% (95% CI)	% (95% CI)
Cellulitis	0	0	3 (13.0)	-13.0 (-32.4, 3.7)	-13.0 (-32.4, 3.1)
Abdominal pain	3 (14.3)	4 (18.2)	8 (34.8)	-20.5 (-44.3, 5.8)	-16.6 (-41.1, 9.9)
Diarrhoea	1 (4.8)	2 (9.1)	6 (26.1)	-21.3 (-43.0, 0.7)	-17.0 (-39.6, 6.3)
Covid-19	6 (28.6)	3 (13.6)	8 (34.8)	-6.2 (-32.8, 21.6)	-21.1 (-44.8, 4.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as any AE events starting or getting worse on or after the first dose of the study drug.

Duration is up to 400 days.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Injection related reaction replaces: Salivary hypersecretion, Chest discomfort, Diarrhoea, and Vomiting.

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

Table 48. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CS3

System Organ Class FMQ (Narrow)	Olezarsen 50 mg N=21 n (%)	Olezarsen 80 mg N=22 n (%)	Placebo N=23 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)					
Thrombocytopenia	2 (9.5)	3 (13.6)	1 (4.3)	5.2 (-13.3, 25.6)	9.3 (-9.7, 30.1)
Anemia	1 (4.8)	3 (13.6)	2 (8.7)	-3.9 (-23.2, 15.6)	4.9 (-15.8, 26.5)
Leukopenia	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Cardiac disorders (SOC)					
Arrhythmia	2 (9.5)	0	0	9.5 (-5.8, 29.2)	0.0 (-14.6, 15.2)
Tachycardia	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Systemic hypertension	1 (4.8)	0	1 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Endocrine disorders (SOC)					
Hypoglycemia	1 (4.8)	1 (4.5)	2 (8.7)	-3.9 (-23.2, 15.6)	-4.2 (-23.3, 14.7)
Hyperglycemia	1 (4.8)	0	3 (13.0)	-8.3 (-28.6, 11.9)	-13.0 (-32.4, 3.1)
Gastrointestinal disorders (SOC)					
Vomiting	1 (4.8)	2 (9.1)	1 (4.3)	0.4 (-17.2, 19.3)	4.7 (-13.6, 24.5)
Dyspepsia	2 (9.5)	2 (9.1)	2 (8.7)	0.8 (-19.3, 22.0)	0.4 (-19.6, 20.9)
Nausea	2 (9.5)	1 (4.5)	1 (4.3)	5.2 (-13.3, 25.6)	0.2 (-17.4, 18.4)
Constipation	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Pancreatitis	2 (9.5)	0	1 (4.3)	5.2 (-13.3, 25.6)	-4.3 (-21.3, 11.1)
Abdominal pain	4 (19.0)	5 (22.7)	8 (34.8)	-15.7 (-40.6, 11.3)	-12.1 (-37.4, 14.9)
Diarrhea	1 (4.8)	2 (9.1)	6 (26.1)	-21.3 (-43.0, 0.7)	-17.0 (-39.6, 6.3)
General disorders and administration site conditions (SOC)					
Local administration reaction	4 (19.0)	4 (18.2)	2 (8.7)	10.4 (-11.5, 33.3)	9.5 (-12.1, 31.8)
Peripheral edema	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Pyrexia	1 (4.8)	1 (4.5)	0	4.8 (-10.2, 23.0)	4.5 (-10.4, 22.1)
Dizziness	1 (4.8)	0	2 (8.7)	-3.9 (-23.2, 15.6)	-8.7 (-27.1, 7.1)
Fatigue	2 (9.5)	1 (4.5)	5 (21.7)	-12.2 (-34.7, 11.1)	-17.2 (-38.6, 3.6)
Hepatobiliary disorders (SOC)					
Hepatic injury	0	2 (9.1)	2 (8.7)	-8.7 (-27.1, 7.8)	0.4 (-19.6, 20.9)

NDA 218614
Tryngolza (olezarsen sodium)

System Organ Class FMQ (Narrow)	Olezarsen 50 mg N=21 n (%)	Olezarsen 80 mg N=22 n (%)	Placebo N=23 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Infections and infestations (SOC)					
Nasopharyngitis	4 (19.0)	3 (13.6)	1 (4.3)	14.7 (-5.3, 36.8)	9.3 (-9.7, 30.1)
Pneumonia	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Purulent material	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Bacterial infection	3 (14.3)	2 (9.1)	5 (21.7)	-7.5 (-30.9, 17.0)	-12.6 (-35.0, 10.0)
Viral infection	10 (47.6)	4 (18.2)	10 (43.5)	4.1 (-24.7, 32.4)	-25.3 (-49.4, 2.1)
Musculoskeletal and connective tissue disorders (SOC)					
Arthralgia	3 (14.3)	1 (4.5)	0	14.3 (-1.4, 34.9)	4.5 (-10.4, 22.1)
Myalgia	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Back pain	1 (4.8)	2 (9.1)	2 (8.7)	-3.9 (-23.2, 15.6)	0.4 (-19.6, 20.9)
Arthritis	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Tendinopathy	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Fracture	0	0	2 (8.7)	-8.7 (-27.1, 7.8)	-8.7 (-27.1, 7.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)					
Malignancy	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Nervous system disorders (SOC)					
Somnolence	1 (4.8)	1 (4.5)	0	4.8 (-10.2, 23.0)	4.5 (-10.4, 22.1)
Dysgeusia	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Paresthesia	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Syncope	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Headache	5 (23.8)	1 (4.5)	4 (17.4)	6.4 (-18.2, 31.3)	-12.8 (-33.8, 7.3)
Psychiatric disorders (SOC)					
Study agent abuse potential	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Anxiety	4 (19.0)	0	0	19.0 (3.0, 40.3) *	0.0 (-14.6, 15.2)
Self-harm	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Depression	1 (4.8)	0	1 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Insomnia	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Renal and urinary disorders (SOC)					
Renal & urinary tract infection	3 (14.3)	1 (4.5)	0	14.3 (-1.4, 34.9)	4.5 (-10.4, 22.1)

NDA 218614
Tryngolza (olezarsen sodium)

System Organ Class FMQ (Narrow)	Olezarsen 50 mg N=21 n (%)	Olezarsen 80 mg N=22 n (%)	Placebo N=23 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Reproductive system and breast disorders (SOC)					
Amenorrhea	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Decreased menstrual bleeding	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Erectile dysfunction	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Sexual dysfunction	1 (4.8)	0	0	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Abnormal uterine bleeding	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Excessive menstrual bleeding	0	0	1 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Respiratory, thoracic and mediastinal disorders (SOC)					
Dyspnea	0	2 (9.1)	1 (4.3)	-4.3 (-21.3, 11.8)	4.7 (-13.6, 24.5)
Bronchospasm	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Cough	3 (14.3)	2 (9.1)	2 (8.7)	5.6 (-15.4, 27.8)	0.4 (-19.6, 20.9)
Skin and subcutaneous tissue disorders (SOC)					
Erythema	2 (9.5)	3 (13.6)	1 (4.3)	5.2 (-13.3, 25.6)	9.3 (-9.7, 30.1)
Alopecia	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Pruritus	2 (9.5)	0	0	9.5 (-5.8, 29.2)	0.0 (-14.6, 15.2)
Rash	1 (4.8)	0	2 (8.7)	-3.9 (-23.2, 15.6)	-8.7 (-27.1, 7.1)
Vascular disorders (SOC)					
Hypotension	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Hemorrhage	3 (14.3)	3 (13.6)	3 (13.0)	1.2 (-20.9, 24.2)	0.6 (-21.3, 23.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as any AE events starting or getting worse on or after the first dose of the study drug.

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. See the table "Patients with Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.2.6. Laboratory Findings, Trial CS3

Results of the FDA analysis of laboratory value abnormalities for Trial CS3 are shown in [Table 49](#). There was an imbalance unfavorable to olezarsen in the proportion of subjects with elevations in fasting plasma glucose Level 1 ≥ 100 mg/dL to 125 mg/dL and Level 2 ≥ 126 mg/dL, as well as low glucose levels < 54 mg/dL and < 40 mg/dL. This risk is further discussed in Section [7.7.4](#).

Table 49. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial CS3

Laboratory Parameter	Olezarsen 50 mg N=21 n/N_w (%)	Olezarsen 80 mg N=22 n/N_w (%)	Placebo N=23 n/N_w (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Sodium, low (mEq/L)					
Level 1 (<132)	2/21 (9.5)	1/22 (4.5)	1/23 (4.3)	5.2 (-13.3, 25.6)	0.2 (-17.4, 18.4)
Level 2 (<130)	2/21 (9.5)	0/22 (0)	0/23 (0)	9.5 (-5.8, 29.2)	0.0 (-14.6, 15.2)
Level 3 (<125)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Sodium, high (mEq/L)					
Level 1 (>150)	1/21 (4.8)	1/22 (4.5)	0/23 (0)	4.8 (-10.2, 23.0)	4.5 (-10.4, 22.1)
Level 2 (>155)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (>160)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Potassium, low (mEq/L)					
Level 1 (<3.6)	5/21 (23.8)	0/22 (0)	2/23 (8.7)	15.1 (-7.5, 38.4)	-8.7 (-27.1, 7.1)
Level 2 (<3.4)	1/21 (4.8)	0/22 (0)	0/23 (0)	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Level 3 (<3)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Potassium, high (mEq/L)					
Level 1 (>5.5)	1/21 (4.8)	2/22 (9.1)	3/23 (13.0)	-8.3 (-28.6, 11.9)	-4.0 (-25.0, 17.3)
Level 2 (>6)	1/21 (4.8)	1/22 (4.5)	1/23 (4.3)	0.4 (-17.2, 19.3)	0.2 (-17.4, 18.4)
Level 3 (>6.5)	0/21 (0)	1/22 (4.5)	0/23 (0)	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Chloride, low (mEq/L)					
Level 1 (<95)	2/21 (9.5)	1/22 (4.5)	0/23 (0)	9.5 (-5.8, 29.2)	4.5 (-10.4, 22.1)
Level 2 (<88)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (<80)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Chloride, high (mEq/L)					
Level 1 (>108)	8/21 (38.1)	7/22 (31.8)	5/23 (21.7)	16.4 (-11.0, 42.1)	10.1 (-16.2, 35.6)
Level 2 (>112)	2/21 (9.5)	0/22 (0)	0/23 (0)	9.5 (-5.8, 29.2)	0.0 (-14.6, 15.2)
Level 3 (>115)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Bicarbonate, low (mEq/L)					
Level 1 (<20)	4/21 (19.0)	2/22 (9.1)	1/23 (4.3)	14.7 (-5.3, 36.8)	4.7 (-13.6, 24.5)
Level 2 (<18)	0/21 (0)	2/22 (9.1)	0/23 (0)	0.0 (-14.6, 15.8)	9.1 (-6.2, 28.1)
Level 3 (<15)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Bicarbonate, high (mEq/L)					
Level 3 (>30)	8/21 (38.1)	9/22 (40.9)	8/23 (34.8)	3.3 (-24.7, 31.1)	6.1 (-21.9, 33.4)

NDA 218614
Tryngolza (olezarsen sodium)

Laboratory Parameter	Olezarsen 50 mg N=21 n/N_w (%)	Olezarsen 80 mg N=22 n/N_w (%)	Placebo N=23 n/N_w (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Glucose, low (mg/dL)					
Level 1 (<70)	11/21 (52.4)	6/22 (27.3)	11/23 (47.8)	4.6 (-24.5, 32.8)	-20.6 (-46.1, 8.1)
Level 2 (<54)	7/21 (33.3)	4/22 (18.2)	3/23 (13.0)	20.3 (-5.0, 44.6)	5.1 (-17.6, 28.2)
Level 3 (<40)	0/21 (0)	2/22 (9.1)	0/23 (0)	0.0 (-14.6, 15.8)	9.1 (-6.2, 28.1)
Glucose, fasting, high (mg/dL)					
Level 1 (≥100 to 125)	11/21 (52.4)	15/22 (68.2)	7/23 (30.4)	21.9 (-7.4, 48.0)	37.7 (8.3, 61.1) *
Level 2 (≥126)	6/21 (28.6)	6/22 (27.3)	5/23 (21.7)	6.8 (-19.1, 32.7)	5.5 (-20.1, 30.9)
Glucose, random, high (mg/dL)					
Level 2 (≥200)	0/7 (0)	0/4 (0)	0/3 (0)	0.0 (-58.7, 37.9)	0.0 (-59.9, 52.8)
Level 3 (>250)	0/7 (0)	0/4 (0)	0/3 (0)	0.0 (-58.7, 37.9)	0.0 (-59.9, 52.8)
Calcium, low (mg/dL)					
Level 1 (<8.4)	2/21 (9.5)	2/22 (9.1)	2/23 (8.7)	0.8 (-19.3, 22.0)	0.4 (-19.6, 20.9)
Level 2 (<8)	1/21 (4.8)	1/22 (4.5)	1/23 (4.3)	0.4 (-17.2, 19.3)	0.2 (-17.4, 18.4)
Level 3 (<7.5)	0/21 (0)	1/22 (4.5)	0/23 (0)	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Calcium, high (mg/dL)					
Level 1 (>10.5)	1/21 (4.8)	0/22 (0)	1/23 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Level 2 (>11)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (>12)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Magnesium, low (mg/dL)					
Level 1 (<1.5)	0/21 (0)	1/22 (4.5)	0/23 (0)	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Level 2 (<1.2)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (<0.9)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Magnesium, high (mg/dL)					
Level 1 (>2.3)	8/21 (38.1)	6/22 (27.3)	10/23 (43.5)	-5.4 (-33.1, 23.4)	-16.2 (-42.1, 12.1)
Level 2 (>4)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (>7)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Phosphate, low (mg/dL)					
Level 1 (<2.5)	4/21 (19.0)	4/22 (18.2)	5/23 (21.7)	-2.7 (-27.0, 22.5)	-3.6 (-27.6, 21.0)
Level 2 (<2)	1/21 (4.8)	0/22 (0)	0/23 (0)	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
Level 3 (<1.4)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Protein, total, low (g/dL)					
Level 1 (<6)	3/21 (14.3)	6/22 (27.3)	8/23 (34.8)	-20.5 (-44.3, 5.8)	-7.5 (-33.7, 19.8)
Level 2 (<5.4)	0/21 (0)	3/22 (13.6)	2/23 (8.7)	-8.7 (-27.1, 7.8)	4.9 (-15.8, 26.5)
Level 3 (<5)	0/21 (0)	1/22 (4.5)	2/23 (8.7)	-8.7 (-27.1, 7.8)	-4.2 (-23.3, 14.7)

NDA 218614
Tryngolza (olezarsen sodium)

Laboratory Parameter	Olezarsen 50 mg N=21 n/N _w (%)	Olezarsen 80 mg N=22 n/N _w (%)	Placebo N=23 n/N _w (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Albumin, low (g/dL)					
Level 1 (<3.1)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 2 (<2.5)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (<2)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
CPK, high (U/L)					
Level 1 (>3X ULN)	1/21 (4.8)	0/22 (0)	2/23 (8.7)	-3.9 (-23.2, 15.6)	-8.7 (-27.1, 7.1)
Level 2 (>5X ULN)	1/21 (4.8)	0/22 (0)	1/23 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Level 3 (>10X ULN)	0/21 (0)	0/22 (0)	1/23 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Blood urea nitrogen, high (mg/dL)					
Level 1 (>23)	6/21 (28.6)	5/22 (22.7)	9/23 (39.1)	-10.6 (-37.0, 17.8)	-16.4 (-41.7, 11.1)
Level 2 (>27)	1/21 (4.8)	0/22 (0)	4/23 (17.4)	-12.6 (-33.6, 8.1)	-17.4 (-37.4, -1.0) *
Level 3 (>31)	1/21 (4.8)	0/22 (0)	2/23 (8.7)	-3.9 (-23.2, 15.6)	-8.7 (-27.1, 7.1)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; ULN, upper limit of normal

Renal-Related Laboratory Values

FDA analysis of renal did not yield clinically significant differences. Further information on the evaluation of olezarsen and renal function is located in Section [17](#).

Table 50. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial CS3

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg N=21 n/N _w (%)	80 mg N=22 n/N _w (%)	N=23 n/N _w (%)	50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Creatinine, high (mg/dL)					
Level 1 (≥1.5X baseline)	3/21 (14.3)	4/22 (18.2)	6/23 (26.1)	-11.8 (-35.5, 13.3)	-7.9 (-32.3, 17.4)
Level 2 (≥2X baseline)	1/21 (4.8)	0/22 (0)	1/23 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Level 3 (≥3X baseline)	1/21 (4.8)	0/22 (0)	0/23 (0)	4.8 (-10.2, 23.0)	0.0 (-14.6, 15.2)
eGFR, low (mL/min/1.73 m ²)					
Level 1 (≥25% decrease)	2/21 (9.5)	2/22 (9.1)	5/23 (21.7)	-12.2 (-34.7, 11.1)	-12.6 (-35.0, 10.0)
Level 2 (≥50% decrease)	0/21 (0)	0/22 (0)	1/23 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.1)
Level 3 (≥75% decrease)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Hematology

Thrombocytopenia leading to bleeding events is a potential antisense oligonucleotide class effect; therefore, analyses evaluated coagulation parameters and platelet levels. Additional hematopoietic parameters were also evaluated. A greater proportion of olezarsen-treated subjects compared to placebo-treated subjects met lower platelet thresholds. This risk is further discussed in Section [7.7.2](#). Another difference of note was a higher proportion of olezarsen-treated subjects had an HbA1c ≥5.7% compared to placebo-treated subjects. Dysglycemia is discussed in Section [7.7.4](#).

Table 51. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial CS3

Laboratory Parameter	Olezarsen 50 mg N=21 n/N_w (%)	Olezarsen 80 mg N=22 n/N_w (%)	Placebo N=23 n/N_w (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
<i>Complete blood count</i>					
WBC, low (10 ³ cells/uL)					
Level 1 (<3.5)	0/21 (0)	4/22 (18.2)	5/23 (21.7)	-21.7 (-42.2, -4.4) *	-3.6 (-27.6, 21.0)
Level 2 (<3)	0/21 (0)	3/22 (13.6)	3/23 (13.0)	-13.0 (-32.4, 3.7)	0.6 (-21.3, 23.0)
Level 3 (<1)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
WBC, high (10 ³ cells/uL)					
Level 1 (>10.8)	5/21 (23.8)	2/22 (9.1)	5/23 (21.7)	2.1 (-23.1, 27.7)	-12.6 (-35.0, 10.0)
Level 2 (>13)	3/21 (14.3)	1/22 (4.5)	1/23 (4.3)	9.9 (-9.3, 31.4)	0.2 (-17.4, 18.4)
Level 3 (>15)	1/21 (4.8)	0/22 (0)	1/23 (4.3)	0.4 (-17.2, 19.3)	-4.3 (-21.3, 11.1)
Hemoglobin, low (g/dL)					
Level 2 (>1.5 g/dL dec. from baseline)	11/21 (52.4)	10/22 (45.5)	16/23 (69.6)	-17.2 (-43.8, 11.8)	-24.1 (-49.6, 5.1)
Level 3 (>2 g/dL dec. from baseline)	8/21 (38.1)	7/22 (31.8)	11/23 (47.8)	-9.7 (-37.2, 19.5)	-16.0 (-42.3, 12.8)
Hemoglobin, high (g/dL)					
Level 2 (>2 g/dL inc. from baseline)	4/21 (19.0)	6/22 (27.3)	4/23 (17.4)	1.7 (-22.1, 26.1)	9.9 (-15.2, 34.5)
Level 3 (>3 g/dL inc. from baseline)	1/21 (4.8)	3/22 (13.6)	2/23 (8.7)	-3.9 (-23.2, 15.6)	4.9 (-15.8, 26.5)
Platelets, low (10 ³ cells/uL)					
Level 1 (<140)	11/21 (52.4)	14/22 (63.6)	8/23 (34.8)	17.6 (-11.8, 44.3)	28.9 (-0.7, 53.8)
Level 2 (<125)	10/21 (47.6)	11/22 (50.0)	7/23 (30.4)	17.2 (-11.8, 43.8)	19.6 (-9.3, 45.6)
Level 3 (<100)	6/21 (28.6)	5/22 (22.7)	5/23 (21.7)	6.8 (-19.1, 32.7)	1.0 (-23.9, 26.1)
Hemoglobin A1C, high (%)					
Level 1 (≥5.7)	11/21 (52.4)	14/22 (63.6)	10/23 (43.5)	8.9 (-20.3, 36.7)	20.2 (-9.2, 46.3)
Level 2 (≥6.5)	4/21 (19.0)	4/22 (18.2)	5/23 (21.7)	-2.7 (-27.0, 22.5)	-3.6 (-27.6, 21.0)
<i>WBC differential</i>					
Lymphocytes, low (10 ³ cells/uL)					
Level 1 (<1)	5/21 (23.8)	10/22 (45.5)	10/23 (43.5)	-19.7 (-45.1, 8.8)	2.0 (-26.4, 30.1)
Level 2 (<0.75)	2/21 (9.5)	4/22 (18.2)	4/23 (17.4)	-7.9 (-29.8, 14.7)	0.8 (-22.7, 24.7)
Level 3 (<0.5)	1/21 (4.8)	2/22 (9.1)	2/23 (8.7)	-3.9 (-23.2, 15.6)	0.4 (-19.6, 20.9)
Lymphocytes, high (10 ³ cells/uL)					
Level 1 (>4)	1/21 (4.8)	1/22 (4.5)	3/23 (13.0)	-8.3 (-28.6, 11.9)	-8.5 (-28.7, 11.0)
Level 2 (>10)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (>20)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)

NDA 218614
Tryngolza (olezarsen sodium)

Laboratory Parameter	Olezarsen 50 mg N=21 n/N_w (%)	Olezarsen 80 mg N=22 n/N_w (%)	Placebo N=23 n/N_w (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Neutrophils, low (10³ cells/uL)					
Level 1 (<2)	5/21 (23.8)	5/22 (22.7)	7/23 (30.4)	-6.6 (-32.3, 20.3)	-7.7 (-33.1, 18.7)
Level 2 (<1)	0/21 (0)	2/22 (9.1)	0/23 (0)	0.0 (-14.6, 15.8)	9.1 (-6.2, 28.1)
Level 3 (<0.5)	0/21 (0)	1/22 (4.5)	0/23 (0)	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)
Eosinophils, high (10³ cells/uL)					
Level 1 (>0.65)	3/21 (14.3)	1/22 (4.5)	4/23 (17.4)	-3.1 (-26.0, 20.6)	-12.8 (-33.8, 7.3)
Level 2 (>1.5)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Level 3 (>5)	0/21 (0)	0/22 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.2)
Coagulation studies					
PT, high (sec)					
Missing	NA	NA	NA	NA	NA
PTT, high (sec)					
Level 1 (>1X ULN)	1/20 (5.0)	2/20 (10.0)	7/23 (30.4)	-25.4 (-47.3, -2.2) *	-20.4 (-43.5, 4.7)
Level 2 (>1.21X ULN)	1/20 (5.0)	0/20 (0)	1/23 (4.3)	0.7 (-17.1, 20.2)	-4.3 (-21.3, 12.4)
Level 3 (>1.41X ULN)	1/20 (5.0)	0/20 (0)	0/23 (0)	5.0 (-10.0, 23.9)	0.0 (-14.6, 16.4)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of patients in treatment arm; n, number of patients meeting criteria; NA, not applicable; Nw, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

7.6.2.7. Assessment of Drug-Induced Liver Injury, Trial CS3

Drug-induced liver injury and hepatic-related AEs are discussed as a Key Safety Review issue in Section [7.7.3](#).

7.6.2.8. Vital-Sign Analyses, Trial CS3

As seen in [Table 52](#) and [Table 53](#), there were no clinically significant patterns or trends observed in abnormalities in blood pressure. Visual inspection of blood pressure, heart rate, respiratory rate, and body temperature graphs by the Clinical Data Scientist review team over time did not identify clinically significant trends.

Table 52. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial CS3

Systolic Blood Pressure (mm Hg)	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=21 n/N _w (%)	N=22 n/N _w (%)	N=23 n/N _w (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
<90	0/21 (0)	0/21 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.8)
≥90	21/21 (100)	21/21 (100)	23/23 (100)	0.0 (-15.8, 14.6)	0.0 (-15.8, 14.6)
≥120	17/21 (81.0)	19/21 (90.5)	17/23 (73.9)	7.0 (-18.8, 31.7)	16.6 (-7.3, 39.3)
≥140	2/21 (9.5)	5/21 (23.8)	6/23 (26.1)	-16.6 (-39.3, 7.3)	-2.3 (-27.8, 24.1)
≥160	0/21 (0)	0/21 (0)	1/23 (4.3)	-4.3 (-21.3, 11.8)	-4.3 (-21.3, 11.8)
≥180	0/21 (0)	0/21 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.8)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Table 53. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial CS3

Diastolic Blood Pressure (mm Hg)	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=21 n/N _w (%)	N=22 n/N _w (%)	N=23 n/N _w (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
<60	0/21 (0)	0/21 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.8)
≥60	21/21 (100)	21/21 (100)	23/23 (100)	0.0 (-15.8, 14.6)	0.0 (-15.8, 14.6)
≥90	4/21 (19.0)	7/21 (33.3)	7/23 (30.4)	-11.4 (-36.2, 15.1)	2.9 (-24.3, 30.2)
≥110	0/21 (0)	1/21 (4.8)	0/23 (0)	0.0 (-14.6, 15.8)	4.8 (-10.2, 23.0)
≥120	0/21 (0)	0/21 (0)	0/23 (0)	0.0 (-14.6, 15.8)	0.0 (-14.6, 15.8)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Table 54. Percentage of Patients Meeting Specific Hypotension Levels Postbaseline, Safety Population, Trial CS3

Blood Pressure (mm Hg)	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=21 n/N _w (%)	N=22 n/N _w (%)	N=23 n/N _w (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
SBP <90	1/21 (4.8)	1/21 (4.8)	0/23 (0)	4.8 (-10.2, 23.0)	4.8 (-10.2, 23.0)
DBP <60	5/21 (23.8)	1/21 (4.8)	6/23 (26.1)	-2.3 (-27.8, 24.1)	-21.3 (-43.0, 0.7)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; SBP, systolic blood pressure

7.6.2.9. Subgroup Analyses, Trial CS3

FDA analysis of AEs by demographic subgroups are shown in [Table 55](#). A difference in AEs across subgroups was not observed. However, the number of subjects is small and therefore the ability to detect meaningful treatment differences across these subgroups is limited.

Table 55. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial CS3

Characteristic	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=21 n/N _s (%)	N=22 n/N _s (%)	N=23 n/N _s (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
Sex					
Female	12/15 (80.0)	11/11 (100)	10/12 (83.3)	-3.3 (-33.3, 29.5)	16.7 (-12.4, 45.5)
Male	6/6 (100)	8/11 (72.7)	11/11 (100)	0.0 (-40.5, 27.1)	-27.3 (-57.2, 3.2)
Age group, years					
<40	6/6 (100)	6/7 (85.7)	8/9 (88.9)	11.1 (-31.8, 44.7)	-3.2 (-44.4, 34.4)
≥40 to <65	11/14 (78.6)	11/13 (84.6)	11/11 (100)	-21.4 (-48.1, 7.9)	-15.4 (-42.9, 13.4)
≥65	1/1 (100)	2/2 (100)	2/3 (66.7)	33.3 (-66.9, 82.7)	33.3 (-51.9, 82.0)
Age group ≥75, years					
≥75	0/0 (NA)	1/1 (100)	0/0 (NA)	NA	NA
Race					
Asian	3/3 (100)	3/3 (100)	0/0 (NA)	NA	NA
Native Hawaiian or other Pacific Islander	0/1 (0)	0/0 (NA)	0/0 (NA)	NA	NA
Other	0/0 (NA)	1/2 (50.0)	1/1 (100)	NA	-50.0 (-93.1, 64.2)
White	15/17 (88.2)	15/17 (88.2)	20/22 (90.9)	-2.7 (-27.2, 18.8)	-2.7 (-27.2, 18.8)
Ethnicity					
Hispanic or Latino	2/3 (66.7)	1/1 (100)	3/3 (100)	-33.3 (-81.5, 40.3)	0.0 (-83.7, 63.1)
Not Hispanic or Latino	16/18 (88.9)	18/21 (85.7)	18/20 (90.0)	-1.1 (-25.0, 21.5)	-4.3 (-26.9, 18.7)
Is in United States					
United States	3/5 (60.0)	6/7 (85.7)	5/7 (71.4)	-11.4 (-59.8, 40.1)	14.3 (-32.2, 55.9)
Non-United States	15/16 (93.8)	13/15 (86.7)	16/16 (100)	-6.3 (-28.8, 14.3)	-13.3 (-38.3, 8.0)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

7.6.2.10. Exposure-Adjusted Analyses, Trial CS3

These analyses were not done as they were unlikely to provide additional meaningful information.

7.6.3. Safety Results, Trial ISIS 678354-CS8

7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial CS8

In Trial CS8, there was a higher proportion of olezarsen-treated subjects experiencing an SAE or discontinuation of study drug due to an AE compared to the placebo-treated subjects ([Table 56](#)). Subjects treated with olezarsen 50 mg reported a higher percentage of study drug discontinuations or modifications due to AEs than the olezarsen 80 mg and placebo treatment groups. However, overall TEAEs were higher in the placebo treatment group (76.9%) versus the olezarsen treatment groups (olezarsen 50 mg, 74.1%; olezarsen 80 mg, 66.7%).

Table 56. Overview of Adverse Events, Safety Population, Trial CS8

Event Category	Olezarsen 50 mg N=58 n (%)	Olezarsen 80 mg N=57 n (%)	Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
SAE	6 (10.3)	8 (14.0)	2 (5.1)	5.2 (-7.8, 16.7)	8.9 (-4.5, 21.3)
SAEs with fatal outcome	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Life-threatening SAEs	0	0	0	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
AE leading to permanent discontinuation of study drug	8 (13.8)	3 (5.3)	0	13.8 (4.3, 25.0) *	5.3 (-4.0, 14.4)
AE leading to dose modification of study drug	6 (10.3)	1 (1.8)	3 (7.7)	2.7 (-11.3, 14.6)	-5.9 (-18.9, 2.8)
AE leading to interruption of study drug	6 (10.3)	1 (1.8)	3 (7.7)	2.7 (-11.3, 14.6)	-5.9 (-18.9, 2.8)
AE leading to reduction of study drug	0	0	0	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
AE leading to dose delay of study drug	0	0	0	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Any AE	43 (74.1)	38 (66.7)	30 (76.9)	-2.8 (-19.6, 15.5)	-10.3 (-27.5, 8.7)
Severe and worse	3 (5.2)	3 (5.3)	1 (2.6)	2.6 (-8.6, 12.1)	2.7 (-8.5, 12.3)
Moderate	22 (37.9)	15 (26.3)	15 (38.5)	-0.5 (-20.3, 18.6)	-12.1 (-31.1, 6.7)
Mild	18 (31.0)	20 (35.1)	14 (35.9)	-4.9 (-24.2, 13.9)	-0.8 (-20.5, 18.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting or getting worse on or after the first dose of the study drug.

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Severity as assessed by the investigator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

7.6.3.2. Deaths, Trial CS8

There was one death in a subject randomized to olezarsen 50 mg in Trial CS8; a brief summary is included here:

- Subject #CS8-(b) (6); CS8 – Death (unknown cause); olezarsen 50 mg Q4W - 76-year-old male in the olezarsen 50 mg group, experienced a severe serious TEAE leading to death (unknown cause) on Study Day 206, approximately 5 weeks after the last dose of olezarsen (Study Day 169). The patient had ongoing coronary artery disease, a cardiac pacemaker insertion, hypertension, hyperlipidemia requiring statin treatment, Type 2 diabetes, and was a former smoker. The patient experienced no liver-related or renal-related laboratory abnormalities with olezarsen treatment during the study. The MACE adjudication committee were unable to determine if the event was a myocardial infarction or heart failure.

Note that another death occurred in Trial CS2, which enrolled a similar population with moderate HTG, with established CVD or at high risk for CVD and is described below:

- Subject #CS2-(b) (6); CS2 – Cardiac arrest, olezarsen 15 mg every 2 weeks – 63-year-old male randomized to olezarsen 15 mg every 2 weeks, experienced a fatal cardiac arrest on Study Day 90, 5 days after the last dose of olezarsen. He had received seven doses of olezarsen before his death. No autopsy was performed. Relevant medical history included type 2 diabetes, acute myocardial infarction, coronary artery bypass graft, coronary revascularization, heart failure, hypertension, and valvular heart disease. At screening, his treated blood pressure was 123/65, and body mass index was 36.6 kg/m² (Class 2 obesity). Concomitant medications included rosuvastatin 40 mg, Vascepa, fenofibrate, Lasix, carvedilol, aspirin, losartan, insulin, canagliflozin, and clopidogrel.

It is difficult to discern olezarsen's contribution, if any, to these deaths especially given the study subjects' age, significant cardiovascular history, and underlying comorbidities.

7.6.3.3. Serious Treatment-Emergent Adverse Events, Trial CS8

In Trial CS8, SAEs occurred in a higher proportion of olezarsen-treated subjects. The biggest treatment difference between olezarsen and placebo-treatment groups were SAEs occurring within the cardiac disorder system organ class (SOC). This risk is discussed further in Section [7.7.7](#). Four subjects in the olezarsen 80 mg group compared to one subject in the placebo group reported an oncological AE. There is temporal plausibility given the time to diagnosis for some of these cases, however, causality cannot be easily determined given the small number of cases and underlying comorbidities – remote smoking history and type 2 diabetes that confound the causality assessment.

Table 57. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CS8

System Organ Class Preferred Term	Olezarsen 50 mg N=58 n (%)	Olezarsen 80 mg N=57 n (%)	Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Any SAE	6 (10.3)	8 (14.0)	2 (5.1)	5.2 (-7.8, 16.7)	8.9 (-4.5, 21.3)
Cardiac disorders (SOC)	3 (5.2)	2 (3.5)	0	5.2 (-4.1, 14.2)	3.5 (-5.7, 12.0)
Angina pectoris	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Tachycardia	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Acute myocardial infarction	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Atrial fibrillation	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Coronary artery disease	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Left ventricular failure	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Gastrointestinal disorders (SOC)	1 (1.7)	1 (1.8)	0	1.7 (-7.4, 9.2)	1.8 (-7.4, 9.4)
Small intestinal obstruction	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Pancreatitis acute	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
General disorders and administration site conditions (SOC)	1 (1.7)	1 (1.8)	0	1.7 (-7.4, 9.2)	1.8 (-7.4, 9.4)
Drug withdrawal syndrome	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Death	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Infections and infestations (SOC)	1 (1.7)	1 (1.8)	0	1.7 (-7.4, 9.2)	1.8 (-7.4, 9.4)
Cellulitis	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Sepsis	1 (1.7)	1 (1.8)	0	1.7 (-7.4, 9.2)	1.8 (-7.4, 9.4)
Injury, poisoning and procedural complications (SOC)	0	1 (1.8)	1 (2.6)	-2.6 (-13.3, 3.8)	-0.8 (-11.7, 7.1)
Tibia fracture	0	1 (1.8)	1 (2.6)	-2.6 (-13.3, 3.8)	-0.8 (-11.7, 7.1)
Head injury	0	0	1 (2.6)	-2.6 (-13.3, 3.8)	-2.6 (-13.3, 3.9)
Ligament sprain	0	0	1 (2.6)	-2.6 (-13.3, 3.8)	-2.6 (-13.3, 3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	4 (7.0)	1 (2.6)	-2.6 (-13.3, 3.8)	4.5 (-6.9, 14.7)
Invasive ductal breast carcinoma	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Non-Hodgkin's lymphoma	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Rectal cancer	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Squamous cell carcinoma of head and neck	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Endometrial cancer stage I	0	0	1 (2.6)	-2.6 (-13.3, 3.8)	-2.6 (-13.3, 3.9)

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System Organ Class Preferred Term	Olezarsen 50 mg N=58 n (%)	Olezarsen 80 mg N=57 n (%)	Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Nervous system disorders (SOC)	0	2 (3.5)	1 (2.6)	-2.6 (-13.3, 3.8)	0.9 (-10.1, 9.8)
Encephalopathy	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Lacunar infarction	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Syncope	0	0	1 (2.6)	-2.6 (-13.3, 3.8)	-2.6 (-13.3, 3.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting or getting worse on or after the first dose of the study drug.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect. Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.3.4. Adverse Events Leading to Treatment Discontinuation, Trial CS8

FDA analysis of AEs and FMQ leading to treatment discontinuation was done. The analysis by SOC and preferred term is shown in [Table 58](#). FMQ analysis is not shown as it did not yield additional relevant information. Eight (13.8%) subjects treated with olezarsen 50 mg and three (5.3%) subjects treated with olezarsen 80 mg discontinued due to an AE compared to no placebo-treated subjects. Half (n=4) of the subjects in the olezarsen 50 mg group discontinued treatment due to events related to the injection site, and one of the three subjects treated with olezarsen 80 mg who discontinued due to an AE did so because of an injection-related reaction (verbatim term 'post-dose flushing - face, neck, chest, lower body'). Further discussion of injection site reactions and hypersensitivity events are found in [Section 7.7.5](#) and [Section 7.7.1](#).

Table 58. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CS8

System Organ Class Preferred Term	Olezarsen 50 mg N=58 n (%)	Olezarsen 80 mg N=57 n (%)	Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Any AE leading to discontinuation	8 (13.8)	3 (5.3)	0	13.8 (4.3, 25.0) *	5.3 (-4.0, 14.4)
Cardiac disorders (SOC)	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Atrial fibrillation	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Gastrointestinal disorders (SOC)	2 (3.4)	0	0	3.4 (-5.7, 11.8)	0.0 (-9.1, 6.4)
Abdominal pain	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Abdominal pain lower	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Dyschezia	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Gastroesophageal reflux disease	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
General disorders and administration site conditions (SOC)	6 (10.3)	0	0	10.3 (0.9, 20.9) *	0.0 (-9.1, 6.4)
Death	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Fatigue	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Injection site erythema	2 (3.4)	0	0	3.4 (-5.7, 11.8)	0.0 (-9.1, 6.4)
Injection site haemorrhage	2 (3.4)	0	0	3.4 (-5.7, 11.8)	0.0 (-9.1, 6.4)
Injection site pruritus	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Injection site urticaria	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Investigations (SOC)	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Urine protein/creatinine ratio abnormal	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Squamous cell carcinoma of head and neck	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Nervous system disorders (SOC)	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Headache	1 (1.7)	0	0	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Vascular disorders (SOC)	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Flushing	0	1 (1.8)	0	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting or getting worse on or after the first dose of the study drug.

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

7.6.3.5. Treatment-Emergent Adverse Events, Trial CS8

Overall, there was a smaller proportion of olezarsen-treated subjects compared to placebo-treated subjects with any TEAE. TEAEs occurring at $\geq 5\%$ frequency are shown in [Table 59](#) below. There were imbalances not favoring both olezarsen treatment groups compared to the placebo group for the following preferred terms that occurred in $\geq 5\%$ of subjects: ‘alanine aminotransferase increased’, ‘diabetes mellitus’, ‘injection site erythema’, ‘COVID-19’, and ‘liver function test increased’. Related topics such as injection site reactions, hepatic-related events, and dysglycemia events are further discussed in [Section 7.7.4](#). Please note that there were imbalances not favoring the placebo treatment group compared to the olezarsen treatment groups such as ‘type 2 diabetes’, ‘sinusitis’, ‘fall’, ‘hypertension’, and ‘urinary tract infection’.

Table 59. Patients With Common Adverse Events Occurring at $\geq 5\%$ Frequency, Safety Population, Trial CS8

Preferred Term	Olezarsen		Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	50 mg N=58 n (%)	80 mg N=57 n (%)		Risk Difference % (95% CI)	Risk Difference % (95% CI)
Any AE	43 (74.1)	38 (66.7)	30 (76.9)	-2.8 (-19.6, 15.5)	-10.3 (-27.5, 8.7)
Alanine aminotransferase increased	3 (5.2)	3 (5.3)	0	5.2 (-4.1, 14.2)	5.3 (-4.0, 14.4)
Diabetes mellitus	4 (6.9)	4 (7.0)	1 (2.6)	4.3 (-7.0, 14.4)	4.5 (-6.9, 14.7)
Injection site erythema	8 (13.8)	2 (3.5)	0	13.8 (4.3, 25.0) *	3.5 (-5.7, 12.0)
Acute sinusitis	1 (1.7)	3 (5.3)	1 (2.6)	-0.8 (-11.7, 7.0)	2.7 (-8.5, 12.3)
Blood creatine phosphokinase increased	0	3 (5.3)	1 (2.6)	-2.6 (-13.3, 3.8)	2.7 (-8.5, 12.3)
COVID-19	5 (8.6)	4 (7.0)	2 (5.1)	3.5 (-9.3, 14.5)	1.9 (-10.7, 12.6)
Liver function test increased	3 (5.2)	1 (1.8)	0	5.2 (-4.1, 14.2)	1.8 (-7.4, 9.4)
Cough	1 (1.7)	3 (5.3)	2 (5.1)	-3.4 (-15.4, 4.8)	0.1 (-12.3, 10.2)
Nasopharyngitis	2 (3.4)	3 (5.3)	2 (5.1)	-1.7 (-13.9, 7.5)	0.1 (-12.3, 10.2)
Back pain	5 (8.6)	1 (1.8)	1 (2.6)	6.1 (-5.5, 16.6)	-0.8 (-11.7, 7.1)
Fatigue	6 (10.3)	1 (1.8)	1 (2.6)	7.8 (-3.9, 18.8)	-0.8 (-11.7, 7.1)
Cellulitis	1 (1.7)	2 (3.5)	2 (5.1)	-3.4 (-15.4, 4.8)	-1.6 (-13.9, 7.7)
Upper respiratory tract infection	1 (1.7)	2 (3.5)	2 (5.1)	-3.4 (-15.4, 4.8)	-1.6 (-13.9, 7.7)
Fall	0	1 (1.8)	2 (5.1)	-5.1 (-17.0, 1.3)	-3.4 (-15.4, 4.9)
Hypertension	2 (3.4)	1 (1.8)	2 (5.1)	-1.7 (-13.9, 7.5)	-3.4 (-15.4, 4.9)
Syncope	0	1 (1.8)	2 (5.1)	-5.1 (-17.0, 1.3)	-3.4 (-15.4, 4.9)
Type 2 diabetes mellitus	1 (1.7)	1 (1.8)	2 (5.1)	-3.4 (-15.4, 4.8)	-3.4 (-15.4, 4.9)
Arthralgia	5 (8.6)	0	2 (5.1)	3.5 (-9.3, 14.5)	-5.1 (-17.0, 1.4)
Dysuria	0	0	2 (5.1)	-5.1 (-17.0, 1.3)	-5.1 (-17.0, 1.4)
Pyelonephritis	0	0	2 (5.1)	-5.1 (-17.0, 1.3)	-5.1 (-17.0, 1.4)
Skin abrasion	0	0	2 (5.1)	-5.1 (-17.0, 1.3)	-5.1 (-17.0, 1.4)
Upper respiratory tract congestion	1 (1.7)	0	2 (5.1)	-3.4 (-15.4, 4.8)	-5.1 (-17.0, 1.4)
Bronchitis	3 (5.2)	0	3 (7.7)	-2.5 (-15.9, 7.9)	-7.7 (-20.4, -1.0) *

Preferred Term	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg N=58 n (%)	80 mg N=57 n (%)		50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Glomerular filtration rate decreased	1 (1.7)	0	3 (7.7)	-6.0 (-18.9, 2.7)	-7.7 (-20.4, -1.0) *
Sinusitis	1 (1.7)	1 (1.8)	4 (10.3)	-8.5 (-22.2, 0.6)	-8.5 (-22.1, 0.7)
Urinary tract infection	6 (10.3)	3 (5.3)	6 (15.4)	-5.0 (-20.8, 8.4)	-10.1 (-25.2, 1.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting or getting worse on or after the first dose of the study drug.

Duration is up to 374 days.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.3.6. Laboratory Findings, Trial CS8

Chemistry

Review of the chemistry laboratory parameters demonstrated an imbalance in the number of subjects with an elevated fasting glucose (Level 1 ≥ 100 to 125 mg/dL). Further discussion of dysglycemia is in Section 7.7.4. No other clinically meaningful differences were observed. See Section 17 for details.

Table 60. Patients With One or More Glucose Values Exceeding Specified Levels, Safety Population, Trial CS8

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg N=58 n/N _w (%)	80 mg N=57 n/N _w (%)		50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Glucose, low (mg/dL)					
Level 1 (<70)	3/58 (5.2)	1/57 (1.8)	1/39 (2.6)	2.6 (-8.6, 12.1)	-0.8 (-11.7, 7.1)
Level 2 (<54)	1/58 (1.7)	0/57 (0)	0/39 (0)	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Level 3 (<40)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Glucose, fasting, high (mg/dL)					
Level 1 (≥ 100 to 125)	17/58 (29.3)	17/57 (29.8)	6/39 (15.4)	13.9 (-3.7, 29.7)	14.4 (-3.3, 30.3)
Level 2 (≥ 126)	41/58 (70.7)	40/57 (70.2)	33/39 (84.6)	-13.9 (-29.7, 3.7)	-14.4 (-30.3, 3.3)
Glucose, random, high (mg/dL)					
Level 2 (≥ 200)	1/12 (8.3)	2/4 (50.0)	1/3 (33.3)	-25.0 (-74.2, 15.5)	16.7 (-52.4, 71.5)
Level 3 (>250)	1/12 (8.3)	1/4 (25.0)	0/3 (0)	8.3 (-51.2, 36.5)	25.0 (-43.8, 72.3)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; N_w, number of patients with data

Hematology

Differences observed in platelet count, lymphocytes, and neutrophils between olezarsen and placebo consisted of a higher proportion of olezarsen-treated subjects meeting a lower threshold values compared to placebo-treated subjects. Additional discussion regarding platelets can be found in Section 7.7.2 and changes in other hematological parameters in Section 17.

Table 61. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial CS8

Laboratory Parameter	Olezarsen	Olezarsen	Placebo N=39 n/N _w (%)	Olezarsen	Olezarsen
	50 mg N=58 n/N _w (%)	80 mg N=57 n/N _w (%)		50 mg vs. Placebo Risk Difference % (95% CI)	
<i>Complete blood count</i>					
WBC, low (10 ³ cells/uL)					
Level 1 (<3.5)	3/58 (5.2)	3/57 (5.3)	1/39 (2.6)	2.6 (-8.6, 12.1)	2.7 (-8.5, 12.3)
Level 2 (<3)	1/58 (1.7)	0/57 (0)	0/39 (0)	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Level 3 (<1)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
WBC, high (10 ³ cells/uL)					
Level 1 (>10.8)	11/58 (19.0)	14/57 (24.6)	7/39 (17.9)	1.0 (-16.1, 16.3)	6.6 (-11.0, 22.6)
Level 2 (>13)	3/58 (5.2)	6/57 (10.5)	3/39 (7.7)	-2.5 (-15.9, 7.9)	2.8 (-11.1, 15.0)
Level 3 (>15)	1/58 (1.7)	4/57 (7.0)	2/39 (5.1)	-3.4 (-15.4, 4.8)	1.9 (-10.7, 12.6)
Hemoglobin, low (g/dL)					
Level 2 (>1.5 g/dL dec. from baseline)	8/58 (13.8)	6/57 (10.5)	5/39 (12.8)	1.0 (-14.7, 14.6)	-2.3 (-17.6, 10.8)
Level 3 (>2 g/dL dec. from baseline)	3/58 (5.2)	5/57 (8.8)	2/39 (5.1)	0.0 (-12.4, 10.0)	3.6 (-9.2, 14.8)
Hemoglobin, high (g/dL)					
Level 2 (>2 g/dL inc. from baseline)	6/58 (10.3)	2/57 (3.5)	1/39 (2.6)	7.8 (-3.9, 18.8)	0.9 (-10.1, 9.8)
Level 3 (>3 g/dL inc. from baseline)	3/58 (5.2)	2/57 (3.5)	1/39 (2.6)	2.6 (-8.6, 12.1)	0.9 (-10.1, 9.8)
Platelets, low (10 ³ cells/uL)					
Level 1 (<140)	10/58 (17.2)	10/57 (17.5)	1/39 (2.6)	14.7 (2.3, 26.9) *	15.0 (2.5, 27.4) *
Level 2 (<125)	5/58 (8.6)	5/57 (8.8)	1/39 (2.6)	6.1 (-5.5, 16.6)	6.2 (-5.3, 16.9)
Level 3 (<100)	0/58 (0)	3/57 (5.3)	1/39 (2.6)	-2.6 (-13.3, 3.8)	2.7 (-8.5, 12.3)
<i>WBC differential</i>					
Lymphocytes, low (10 ³ cells/uL)					
Level 1 (<1)	13/58 (22.4)	9/57 (15.8)	4/39 (10.3)	12.2 (-3.8, 26.5)	5.5 (-9.8, 19.1)
Level 2 (<0.75)	4/58 (6.9)	4/57 (7.0)	0/39 (0)	6.9 (-2.4, 16.5)	7.0 (-2.3, 16.8)
Level 3 (<0.5)	1/58 (1.7)	0/57 (0)	0/39 (0)	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Lymphocytes, high (10 ³ cells/uL)					
Level 1 (>4)	2/58 (3.4)	4/57 (7.0)	4/39 (10.3)	-6.8 (-20.6, 3.3)	-3.2 (-17.5, 8.4)
Level 2 (>10)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (>20)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs. Placebo	
	N=58	N=57	N=39	Risk Difference	Risk Difference
	n/N _w (%)	n/N _w (%)	n/N _w (%)	% (95% CI)	% (95% CI)
Neutrophils, low (10³ cells/uL)					
Level 1 (<2)	6/58 (10.3)	6/57 (10.5)	2/39 (5.1)	5.2 (-7.8, 16.7)	5.4 (-7.6, 17.0)
Level 2 (<1)	1/58 (1.7)	2/57 (3.5)	0/39 (0)	1.7 (-7.4, 9.2)	3.5 (-5.7, 12.0)
Level 3 (<0.5)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Eosinophils, high (10³ cells/uL)					
Level 1 (>0.65)	2/58 (3.4)	7/57 (12.3)	4/39 (10.3)	-6.8 (-20.6, 3.3)	2.0 (-12.9, 15.0)
Level 2 (>1.5)	1/58 (1.7)	2/57 (3.5)	1/39 (2.6)	-0.8 (-11.7, 7.0)	0.9 (-10.1, 9.8)
Level 3 (>5)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Coagulation studies					
PT, high (sec)					
Level 1 (>1.1X ULN)	5/56 (8.9)	1/54 (1.9)	5/39 (12.8)	-3.9 (-19.0, 8.9)	-11.0 (-25.2, -0.9) *
Level 2 (>1.3X ULN)	2/56 (3.6)	0/54 (0)	2/39 (5.1)	-1.6 (-13.8, 7.9)	-5.1 (-17.0, 1.8)
Level 3 (>1.5X ULN)	1/56 (1.8)	0/54 (0)	1/39 (2.6)	-0.8 (-11.7, 7.3)	-2.6 (-13.3, 4.2)
PTT, high (sec)					
Level 1 (>1X ULN)	6/56 (10.7)	1/54 (1.9)	4/39 (10.3)	0.5 (-14.3, 13.2)	-8.4 (-22.1, 1.1)
Level 2 (>1.21X ULN)	3/56 (5.4)	0/54 (0)	1/39 (2.6)	2.8 (-8.4, 12.5)	-2.6 (-13.3, 4.2)
Level 3 (>1.41X ULN)	1/56 (1.8)	0/54 (0)	1/39 (2.6)	-0.8 (-11.7, 7.3)	-2.6 (-13.3, 4.2)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

Hepatic-Related Parameters

Higher proportions of subjects treated with olezarsen met ALT and AST thresholds >3x ULN but <5x ULN. Further discussion of hepatic-related AEs is found in Section [7.7.3](#).

Table 62. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial CS8

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs. Placebo	80 mg vs. Placebo
	N=58	N=57	N=39	Risk Difference	Risk Difference
	n/N _w (%)	n/N _w (%)	n/N _w (%)	% (95% CI)	% (95% CI)
Alkaline phosphatase, high (U/L)					
Level 1 (>1.5X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 2 (>2X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (>3X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Alanine aminotransferase, high (U/L)					
Level 1 (>3X ULN)	4/58 (6.9)	1/57 (1.8)	0/39 (0)	6.9 (-2.4, 16.5)	1.8 (-7.4, 9.4)
Level 2 (>5X ULN)	2/58 (3.4)	0/57 (0)	0/39 (0)	3.4 (-5.7, 11.8)	0.0 (-9.1, 6.4)
Level 3 (>10X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs.	80 mg vs.
	N=58	N=57	N=39	Placebo	Placebo
	n/N _w (%)	n/N _w (%)	n/N _w (%)	Risk Difference	Risk Difference
				% (95% CI)	% (95% CI)
Aspartate aminotransferase, high (U/L)					
Level 1 (>3X ULN)	3/58 (5.2)	0/57 (0)	0/39 (0)	5.2 (-4.1, 14.2)	0.0 (-9.1, 6.4)
Level 2 (>5X ULN)	1/58 (1.7)	0/57 (0)	0/39 (0)	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Level 3 (>10X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Bilirubin, total, high (mg/dL)					
Level 1 (>1.5X ULN)	0/58 (0)	0/57 (0)	1/39 (2.6)	-2.6 (-13.3, 3.8)	-2.6 (-13.3, 3.9)
Level 2 (>2X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (>3X ULN)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot..."

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

7.6.3.7. Assessment of Drug-Induced Liver Injury, Trial CS8

Drug-induced liver injury and hepatic-related AEs are discussed as a Key Safety Review issue in Section [7.7.3](#).

7.6.3.8. Vital-Sign Analyses, Trial CS8

Review of the FDA analysis of vital signs did not demonstrate a significance difference between treatment groups.

Table 63. Percentage of Patients with Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial CS8

Systolic Blood Pressure (mm Hg)	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs.	80 mg vs.
	N=58	N=57	N=39	Placebo	Placebo
	n/N _w (%)	n/N _w (%)	n/N _w (%)	Risk Difference	Risk Difference
				% (95% CI)	% (95% CI)
<90	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
≥90	58/58 (100)	57/57 (100)	39/39 (100)	0.0 (-6.3, 9.1)	0.0 (-6.4, 9.1)
≥120	57/58 (98.3)	57/57 (100)	39/39 (100)	-1.7 (-9.2, 7.4)	0.0 (-6.4, 9.1)
≥140	26/58 (44.8)	31/57 (54.4)	20/39 (51.3)	-6.5 (-26.1, 13.7)	3.1 (-16.9, 23.0)
≥160	8/58 (13.8)	5/57 (8.8)	5/39 (12.8)	1.0 (-14.7, 14.6)	-4.0 (-19.1, 8.6)
≥180	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 64. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial ISIS-678354-CS8

Diastolic Blood Pressure (mm Hg)	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=58 n/N _w (%)	N=57 n/N _w (%)	N=39 n/N _w (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
<60	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
≥60	58/58 (100)	57/57 (100)	39/39 (100)	0.0 (-6.3, 9.1)	0.0 (-6.4, 9.1)
≥90	19/58 (32.8)	18/57 (31.6)	12/39 (30.8)	2.0 (-17.3, 20.2)	0.8 (-18.5, 19.0)
≥110	1/58 (1.7)	2/57 (3.5)	1/39 (2.6)	-0.8 (-11.7, 7.0)	0.9 (-10.1, 9.8)
≥120	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 65. Percentage of Patients Meeting Specific Hypotension Levels Postbaseline, Safety Population, Trial CS8

Blood Pressure (mm Hg)	Olezarsen 50 mg	Olezarsen 80 mg	Placebo	Olezarsen 50 mg vs. Placebo	Olezarsen 80 mg vs. Placebo
	N=58 n/N _w (%)	N=57 n/N _w (%)	N=39 n/N _w (%)	Risk Difference % (95% CI)	Risk Difference % (95% CI)
SBP <90	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
DBP <60	5/58 (8.6)	7/57 (12.3)	8/39 (20.5)	-11.9 (-28.1, 2.0)	-8.2 (-24.9, 6.6)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; SBP, systolic blood pressure

7.6.3.9. Subgroup Analyses, Trial CS8

Subgroup safety analyses in this supportive safety trial was not done.

7.6.3.10. Exposure-Adjusted Analyses, Trial CS8

Exposure-adjusted analyses were not done for Trial CS8.

7.7. Key Safety Review Issues

7.7.1. Hypersensitivity Reactions

Issue

Serious hypersensitivity reactions have occurred with olezarsen treatment, it is unclear whether there is a relationship to the development of anti-olezarsen antibodies or previous volanesorsen treatment.

Background

Hypersensitivity reactions is a known and labeled adverse drug reaction for several FDA-approved ASOs. As of 2023, there have been 10 ASOs approved for a variety of medical diseases. Hypersensitivity reactions are listed in the Warnings & Precautions section of labeling for four of these drugs – defibrotide, inotersen, eteplirsen, and golodirsen. The types of reactions observed include rash, urticaria, skin exfoliation, chills, flushing, dysphagia, tachycardia, and bronchospasm. Serious hypersensitivity reactions were noted to occur in the clinical development program for volanesorsen, including an anaphylactic-like reaction in a study subject without FCS within 5 minutes of dosing which required emergency treatment ([EMDAC 2018](#)).

Assessment

In this review, hypersensitivity events were evaluated in categories defined as flu-like reactions and hypersensitivity reactions using a variety of company, FDA, and MedDRA queries.

Flu-like reactions (FLR) were defined as the following:

- FLR 1 – influenza-like illness, pyrexia, feeling hot, body temperature increased, chills, myalgia, or arthralgia starting on day of injection or next day.
- FLR 2 – (A) influenza-like illness or (B) pyrexia, feeling hot, or body temperature increased, plus two of the following: chills, myalgia, or arthralgia starting on day of injection or next day.

Hypersensitivity reactions were defined using the following:

- Hypersensitivity Standardised MedDRA Query (SMQ) (narrow),
- Hypersensitivity FMQ (narrow, broad, algorithmic⁴) and
- Anaphylactic FMQ (narrow).

An AE of special interest was defined as a requirement of any use of medications as pretreatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction.

[Table 66](#) is an overview of the phase 2/3 trials which combines the hypersensitivity events and flu-like reactions, followed by a breakdown of the types of each event in Trials CS3 and CS8. Serious events or events that led to study drug discontinuation from these trials are discussed.

Table 66. Overview of Hypersensitivity and Flu-Like Reactions, All Phase 2/3 Trials

Adverse Event Type	CS3			CS8			CS13 ³	CS7
	OLZ 50 N=21 n (%)	OLZ 80 N=22 n (%)	PBO N=23 n (%)	OLZ 50 N=58 n (%)	OLZ 80 N=57 n (%)	PBO N=39 n (%)	OLZ N=54 n (%)	OLZ N=24 n (%)
Hypersensitivity/FLR/ TEAE	3 (14.3)	3 (13.6)	3 (13.0)	5 (8.6)	1 (1.8)	0	8 (14.8)	7 (29)
FLR	1 (4.8)	1 (4.5)	0	0	0	0	2 (3.7)	4 (16.7)
Hypersensitivity ^{1,2}	3 (14.3)	2 (9.0)	3 (13.0)	5 (8.6)	1 (1.8)	0	7 (13.0)	3 (12.5)

⁴ As hypersensitivity can manifest itself across multiple organ systems, the algorithmic strategy is based on the locations that hypersensitivity is known to commonly affect, i.e., airway, skin, soft tissue, and systemic with start dates within 7 days of dosing.

Adverse Event Type	CS3			CS8			CS13 ³	CS7
	OLZ 50 N=21 n (%)	OLZ 80 N=22 n (%)	PBO N=23 n (%)	OLZ 50 N=58 n (%)	OLZ 80 N=57 n (%)	PBO N=39 n (%)	OLZ N=54 n (%)	OLZ N=24 n (%)
Serious hypersensitivity/FLR/AE	0	0	0	0	0	0	2 (3.7)	1 (4.2)
Discontinuation due to hypersensitivity/FLR AE	0	2 (9.0)	0	1 (1.7)	1 (1.8)	0	2 (3.7)	1 (4.2)
AESI – pretreatment	1 (4.8)	0	0	0	0	0	1 (1.8)	0

Source: Adapted from CSR CS3 Tables 42, 48; CSR CS8 Tables 46; CSR CS13 Tables 35, 37; CSR CS7 Tables 37, 38; adae.xpt CS3, CS8, CS13, CS7

1. CS3; CS8 Hypersensitivity includes Hypersensitivity SMQ (narrow), FMQ, Anaphylactic reaction FMQ

2. CS13, CS7: Hypersensitivity by Hypersensitivity SMQ (narrow)

3. CS13: Subjects with an event starting in the OLE study (i.e., subjects with events that occurred in the index study are not included)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CSR, clinical study report; FLR, flu-like reaction; FMQ, FDA medical query; MedDRA; Medical Dictionary for Regulatory Activities; OLE, open-label extension; OLZ, olezarsen; PBO, placebo; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event

In Trials CS3 and CS8, the number of subjects with hypersensitivity events were similar. There were two subjects in CS3 with a flu-like reaction (with one leading to discontinuation) and none in the placebo group. There were no serious hypersensitivity events or flu-like reactions, although three subjects treated with olezarsen (one in CS3 and two in CS8) discontinued treatment due to a hypersensitivity event. [Table 67](#) below lists the hypersensitivity AEs and FLR in Trials CS3 and CS8.

Table 67. Hypersensitivity and Flu-Like Reaction TEAEs, Safety Set, Trials CS3 and CS8

Adverse Event Type	Trial CS3			Trial CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
Hypersensitivity SMQ (narrow)	2 (9.5)	1 (4.5)	3 (13.0)	3 (5.2)	0	0
Injection-related reaction ^a	1 (4.8)	1 (4.5)	0	0	0	0
Dermatitis	1 (4.8)	0	1 (4.3)	0	0	0
Eczema	0	0	1 (4.3)	0	0	0
Rash macular ^b	0	0	1 (4.3)	0	0	0
Injection site urticaria ^b	0	0	0	1 (1.7)	0	0
Dermatitis contact	0	0	0	1 (1.7)	0	0
Rash ^b	0	0	0	1 (1.7)	0	0

Adverse Event Type	Trial CS3			Trial CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
Hypersensitivity FMQ broad	2 (9.5)	2 (9.1)	1 (4.3)	5 (8.6)	1 (1.8)	0
Asthma	0	0	0	1 (1.7)	0	0
Blood pressure decreased	0	0	0	1 (1.7)	0	0
Flushing	1 (4.8)	1 (4.5)	0	0	1 (1.8)	1 (0.9)
Pruritus	1 (4.8)	0	0	1 (1.7)	0	0
Rash macular ^b	0	0	1 (4.3)	0	0	0
Swelling ^c	0	1 (4.5)	0	0	0	0
Injection site urticaria ^b	0	0	0	1 (1.7)	0	0
Pruritus	0	0	0	1 (1.7)	0	0
Rash ^b	0	0	0	1 (1.7)	0	0
Serious hypersensitivity TEAE	0	0	0	0	0	0
Discontinuation due to hypersensitivity TEAE	0	1 (4.5)	0	1 (1.7)	1 (1.8)	0
AESI – pretreatment	0	0	0	0	0	0
FLR	1 (4.8)	1 (4.5)	0	0	0	0
Arthralgia	0	1 (4.5)	0	0	0	0
Chills	1 (4.8)	1 (4.5)	0	0	0	0
Myalgia	0	1 (4.5)	0	0	0	0
Serious FLR TEAE	0	0	0	0	0	0
Discontinuation due to FLR TEAE	0	1 (4.5)	0	0	0	0

Source: Adapted from CSR CS3 Tables 42, 48; CSR CS8 Tables 46 Confirmed by review of adae.xpt

^a Injection related reaction replaces the preferred terms Salivary hypersecretion, Chest discomfort, Diarrhoea, and Vomiting. These events occurred during or 15 minutes after study drug injection and therefore were recoded as injection-related reaction events.

^b The same events were captured in both the Hypersensitivity SMQ (narrow) and Hypersensitivity FMQ (broad)

^c The review of this adverse event noted that that swelling resulted from an injury to the head and in this reviewer's opinion should not be considered a hypersensitivity event.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CSR, clinical study report; FLR, flu-like reaction; FMQ, FDA medical query; MedDRA; Medical Dictionary for Regulatory Activities; OLE, open-label extension; OLZ, olezarsen; PBO, placebo; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event

In the ongoing open-label trials, CS7 and CS13, there were additional hypersensitivity and FLR events observed (hypersensitivity SMQ [narrow] CS7 [n=3; 12.5%] and CS13 [n=7; 13%]; FLR CS7 [n=4, 16.7%] and CS13 [n=2; 3.7%]).

Among Trials CS3, CS8, CS13, and CS13, there were seven subjects who discontinued due to hypersensitivity or FLR. Three of these discontinuations were considered serious TEAEs, including one serious 'anaphylactic reaction'. The narratives of these subjects were reviewed and are summarized in tabular form in Section 17. Summaries of the serious hypersensitivity events are included below.

Serious Hypersensitivity Events

- Subject (b) (6), Trial CS7 – 'Hypersensitivity Reaction': 62-year-old female with FCS. She had been previously treated with volanesorsen for 5 years. Her last dose of volanesorsen was approximately 9 months before starting olezarsen 80 mg Q4W in the open-label trial, CS7. Within 10 hours of administration of her 2nd dose of olezarsen, she reported an itchy

rash on her back. Two days later she reported flu-like symptoms (runny nose, headache, sore throat, and fatigue), progressive whole-body rash, wheezing, stiff neck, swelling of the eyes and face, and dyspnea. She did not seek any additional medical attention and reported treatment with loratadine 10 mg and fexofenadine hydrochloride 180 mg. Approximately 10 days after the start of the event, the swelling resolved and treatment was permanently discontinued. Her ADA titers remained negative.

- Subject (b) (6), Trial CS13 – ‘Hypersensitivity Reaction’: 56-year-old male with FCS, previously treated with volanesorsen for 4 months and reported an immunization reaction – with injection site discoloration, injection site erythema with occurrence of positive ADA (peak titer 6000). No further volanesorsen treatment was received.

This subject’s first dose of olezarsen occurred in the OLE study (randomized to placebo in parent study CS3). ADA titers at the beginning of the OLE were 800. Approximately two minutes after the administration of the second dose of olezarsen, the subject exhibited an intense redness of his face and trunk, which was accompanied by an intense headache. He did not present with dyspnea or fainting at this time. The subject’s vital parameters were immediately checked and were as follows: BP of 107/70 mmHg, heart rate (HR) of 72 bpm, and no dyspnea on room air with 88% oxygen saturation (SpO₂). The patient did not go to the emergency room or hospital but was treated at the study site with IV saline and 4 mg betamethasone intramuscularly. Monitoring of the patient continued. Resolution of the skin rash was noted after approximately 10 minutes post onset of symptoms. The investigator noted the appearance of a wheal reaction with redness in correspondence to the patient’s abdomen area (periumbilical region and under the right rib) which was associated with intense itching. Approximately 20 minutes after symptoms began, the patient’s SpO₂ (98%) and BP (127/85 mmHg) had returned to normal. Treatment with chlorpheniramine maleate was administered intravenously to treat the itching. An hour after the onset of hypersensitivity, the patient experienced bronchospasm and shaking chills. Treatment included a single dose of methylprednisolone with a combination of beclomethasone dipropionate, ipratropium bromide and salbutamol which resulted in an improvement of symptoms. An ECG showed no abnormalities. Laboratory values of hsCRP, C3, C4, absolute eosinophil count and tryptase before and 1.5 hours after the event were normal. ADA following second dose increased to 6400. The subject’s condition improved, and he was discharged from the study site on the same day in good clinical condition.

- Subject (b) (6), Trial CS13 – ‘Anaphylactic reaction’: 26-year-old male with FCS, previously treated with volanesorsen in Trial CS7, an open-label extension study. In CS7-OLE, he received 24 doses of volanesorsen 300 mg weekly and had a positive ADA titer in (b) (6) (last assessment) of 400. He enrolled in Trial CS3 (baseline ADA positive titer 400) and was treated with olezarsen 80 mg for 1 year and rolled into the open-label study, CS13 (ADA titer at baseline 25,600). Forty-five minutes after each of the first two injections of olezarsen in the OLE trial, he experienced chills, headache, and diffuse abdominal discomfort lasting 30 minutes to 1 hour, and approximately 2 to 3 hours of diffuse muscle tenderness. Because of these symptoms, the subject was pre-treated with 40 mg of prednisolone and 500 mg of Tylenol for subsequent injections without further difficulty until the 7th dose. Following his dose of prednisolone and olezarsen, he left the study site in stable condition, but returned within 5 minutes because of acute onset of profuse diaphoresis, facial edema, diffuse erythema, and severe low back pain. He was brought to the emergency department and administered IV Benadryl, solumedrol 125 mg, dexamethasone 10 mg,

famotidine 10 mg, and fluids. Vitals at the time were BP of 140 to 160 mmHg (note at screening for CS13 – the subject’s BP was 167/107 mmHg), HR 110 bpm, and oxygen saturation of 94%. ECG showed sinus tachycardia with non-specific ST-T abnormalities. Tryptase was 5.0 before dose, 4 hours later 10.7 (normal <11). On the same day, he recovered from the event and was discharged from the ER with a dexamethasone taper. The study drug was discontinued due to this event. His ADA titers remained positive. At the time of this event, his ADA titers were 6400 and, in the weeks, following increased to 12,800. Approximately 2 months after his last dose ADA titers were 200.

Reviewer Comment

This event was submitted to the IND as a 7-day suspected unexpected serious adverse reaction. At that time, an internal consult with the Division of Pulmonology, Allergy, and Critical Care was requested for review of this event. Following review of the information, the Division of Pulmonology, Allergy, and Critical Care review team felt this event was more consistent with an acute injection-related reaction versus anaphylaxis (Document Archiving, Reporting and Regulatory Tracking System [DARRTS] ID 5100318).

Conclusion

Hypersensitivity reactions, including serious events, occur in patients with FCS treated with olezarsen. The onset of symptoms usually occurs within minutes or same day of the injection. There is a variable length of treatment duration before the event (first couple of doses versus years of exposure). The numbers of hypersensitivity and FLR events overall are very small, so their dependence on ADA is unclear. Of the three serious cases, ADA values appear to increase in two cases before the event. There were only two cases of subjects receiving pre-treatment to avoid a hypersensitivity reaction, and both times this did not prevent events. Pre-treatment is not recommended given no systematic protocol for pre-treatment was provided or prospectively tested. It is anticipated that additional potentially serious hypersensitivity reactions will occur in individuals with FCS treated with olezarsen. Serious hypersensitivity reactions are a known adverse drug reaction for this drug class. Management of this risk through labeling with revisions to include the types of signs and symptoms observed is a reasonable mitigation.

7.7.2. Platelet Reductions and Bleeding Events

Issue

In the clinical trials, olezarsen-treated subjects experienced a higher frequency of platelet reductions compared to placebo-treated subjects, although none were severe (defined as $<50 \times 10^9/L$). However, because of the exclusion of study subjects with baseline platelet counts below $100 \times 10^9/L$, it is unknown whether serious thrombocytopenia events will occur in patients with FCS, a patient population with reported platelet variability who may have below normal platelet counts at the beginning of treatment in the postapproval setting.

Background

Anti-sense oligonucleotides are associated with thrombocytopenia and risk of serious bleeding, including fatal hemorrhage complications ([Benson et al. 2018](#); [Dominguez Senin et al. 2022](#)). The primary safety concern for volanesorsen (which shares the same oligonucleotide sequence as

olezarsen) was severe thrombocytopenia and risk of serious bleeding ([EMDAC 2018](#)). Although no deaths or serious bleeding events were noted in the volanesorsen clinical development program, there was a higher proportion of volanesorsen-treated subjects with clinical bleeding events (excluding bleeding at the injection site) than placebo-treated subjects (36% versus 6%, respectively). Reductions in platelet counts associated with volanesorsen were characterized by gradual declines over time of approximately 30% from baseline as well as large precipitous drops in platelet count below $50 \times 10^9/L$. The mechanism triggering these events is unknown but may be a result of drug-induced immune thrombocytopenia leading to increased destruction of platelets.

Given the concern for thrombocytopenia, the pivotal FCS trial excluded study subjects that had a baseline platelet count below $100 \times 10^9/L$ ($>140 \times 10^9/L$ was considered the lower bound of a normal platelet count) and instituted frequent platelet monitoring (every 2 weeks). Note, no subject was excluded during the screening process due to a platelet count $<100 \times 10^9/L$. In CS8, platelet levels were obtained Q4W; in CS7 initially every 2 weeks for first 13 weeks then Q4W, and in CS13 Q4W, 8 weeks, and 12 weeks in the 1st, 2nd, and 3rd years, respectively. All protocols had pre-specified actions for platelet counts below different platelet count thresholds below $100 \times 10^9/L$. An adverse event of special interest was defined as any case of a platelet count reduction below $50 \times 10^9/L$ accompanied by a major or clinically relevant bleeding event, or platelet count below $25 \times 10^9/L$.

Assessment

Baseline Platelet Values

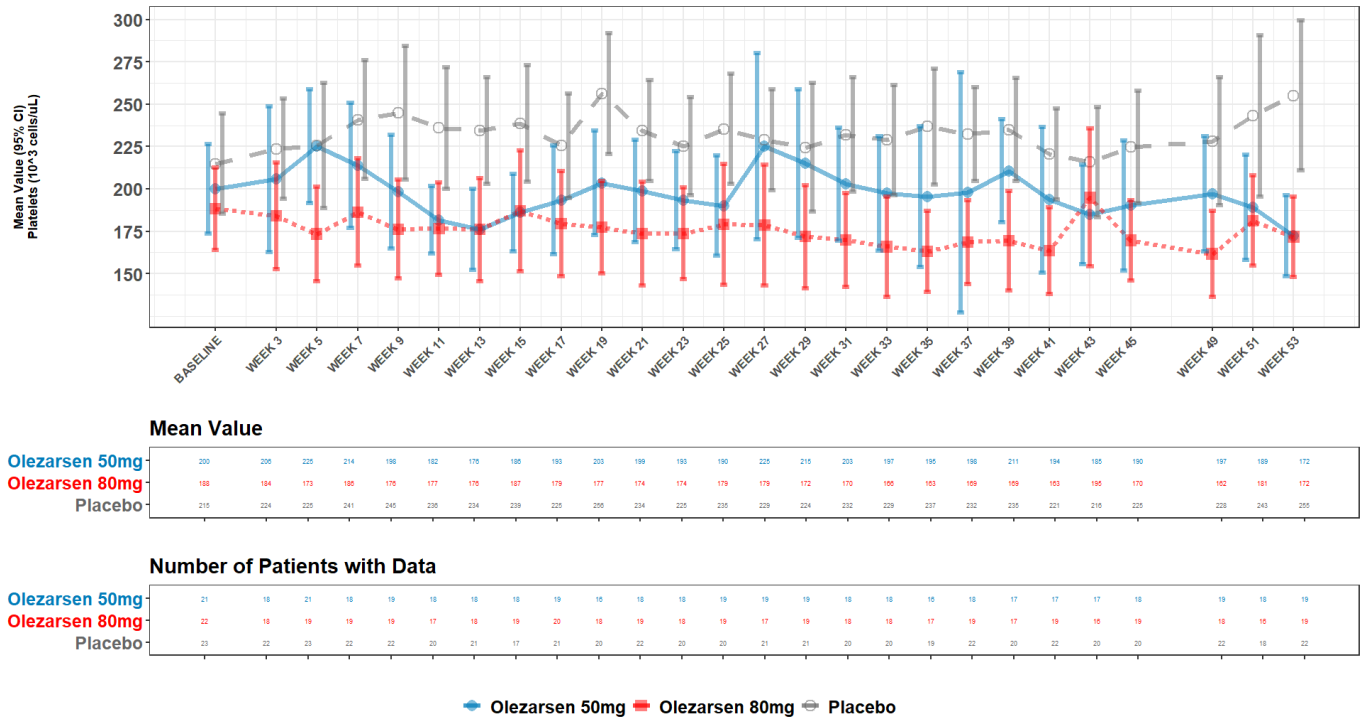
Given the reported platelet variability in individuals with FCS, the baseline platelet count was defined as the average of all assessments before the first dose of study drug. The average baseline level of platelets in CS3 was 200, 188, and $215 \times 10^9/L$ in the olezarsen 50 mg, 80 mg, and placebo groups, respectively. The mean baseline level of platelets in CS8 was 244, 249, and $252 \times 10^9/L$ in the olezarsen 50 mg, 80 mg, and placebo groups, respectively.

Platelet Values Over Time

As shown in the [Figure 11](#) and [Figure 12](#) below, platelets decreased over time for the subjects in the olezarsen groups compared to those in the placebo group during CS3. Average declines in platelet count of approximately 5 to 15% from baseline were noted in the olezarsen treatment groups. There were 11 (25.6%) olezarsen-treated subjects and 5 (21.7%) placebo-treated subjects that had platelet counts that went below $100 \times 10^9/L$. In CS3, there were 4 (18.2%) subjects treated with olezarsen 80 mg and 1 (4.3%) placebo-treated subject with dose interruptions due to low platelet count.

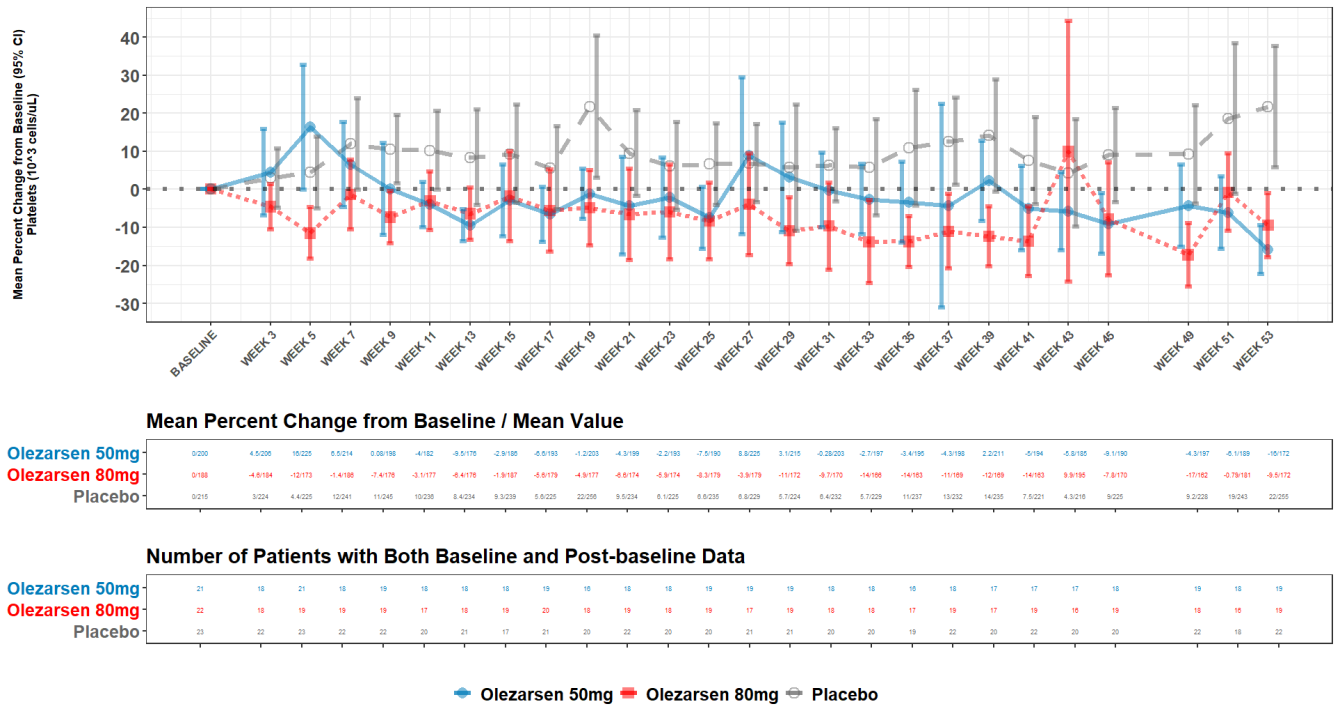
By visual inspection of [Figure 11](#) and [Figure 13](#) from CS3 and CS8, respectively, of mean platelet count over time, it appears that platelet counts gradually decline over the first 9 months and then appear to stabilize, although there is significant variability at some timepoints in the FCS population.

Figure 11. Mean Platelet Counts Over Time, Safety Set, Trial CS3



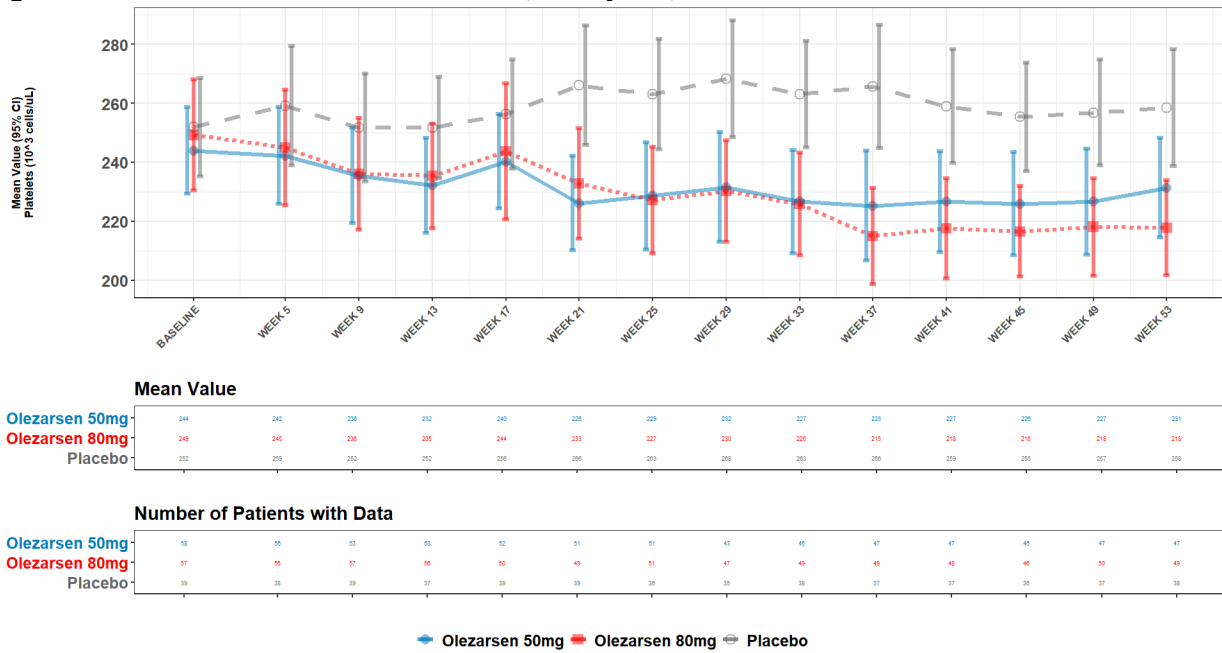
Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval

Figure 12. Platelets - Mean Percent Change From Baseline, Safety Set, Trial CS3



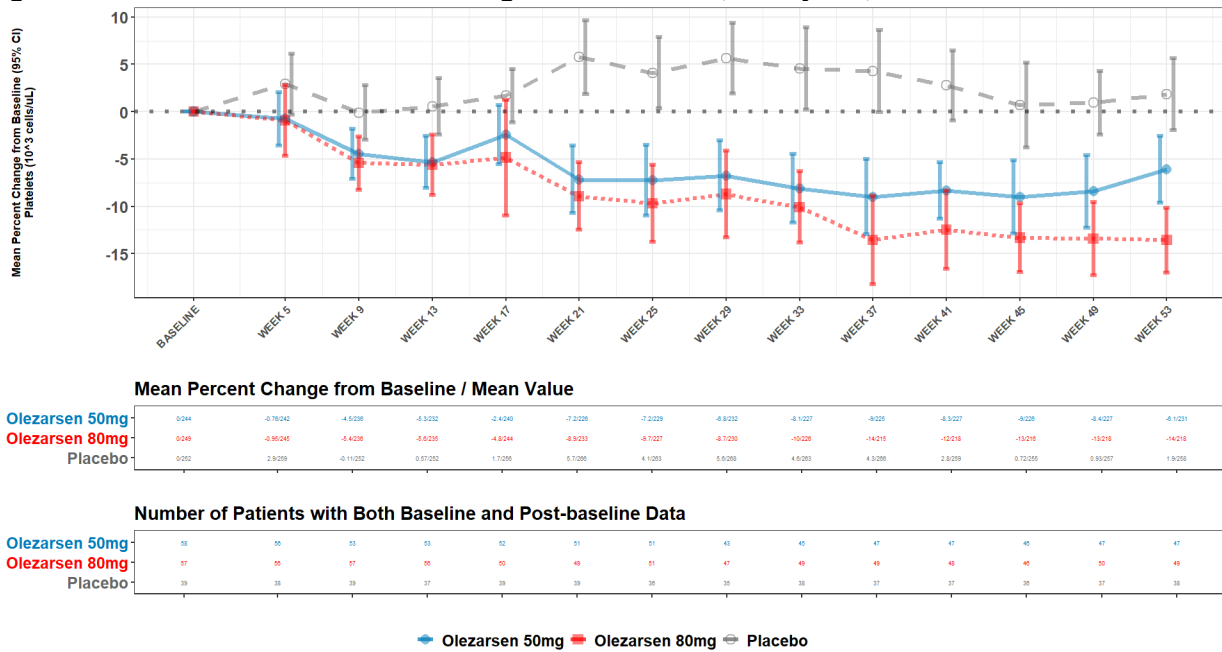
Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval

Figure 13. Mean Platelet Counts Over Time, Safety Set, Trial CS8



Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval

Figure 14. Platelets - Mean Percent Change From Baseline, Safety Set, Trial CS8



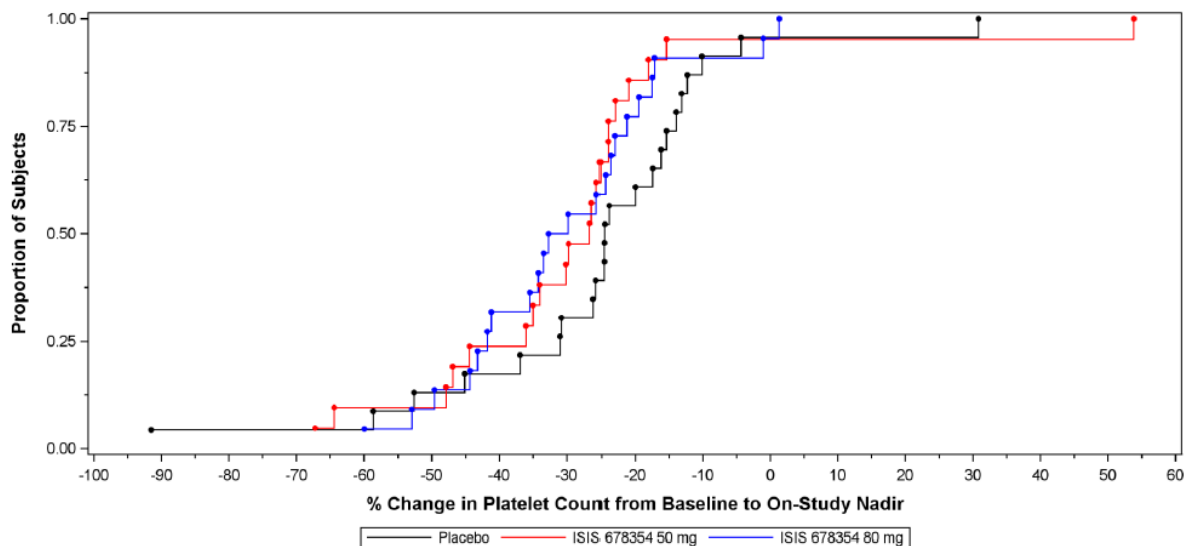
Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval

Categorical Changes in Platelet Values

A higher proportion of subjects treated with olezarsen exhibited categorical absolute or relative reductions in platelet count compared to subjects treated with placebo in both CS3 and CS8. In CS3, almost 50% of subjects treated with olezarsen versus 30% of placebo-treated subjects had a 30% reduction in platelet counts from baseline. In CS8, roughly 20% of olezarsen versus 5% of placebo-treated subjects had a 30% reduction in platelet counts from baseline. However, the percentage of subjects with 50% reductions from baseline were similar across treatment groups in both trials.

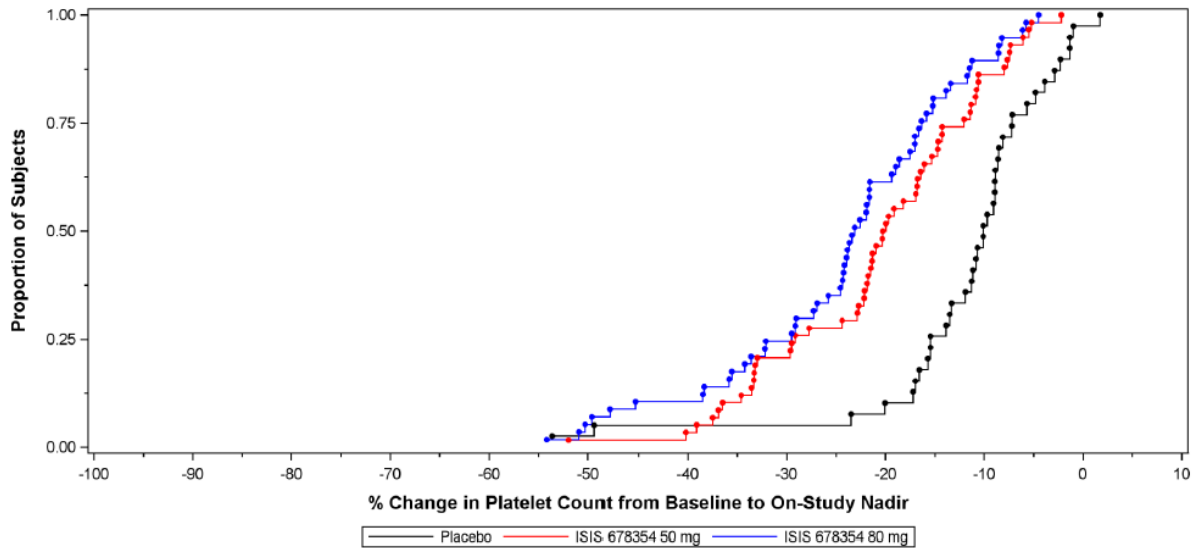
The empirical cumulative distribution functions for percent change from baseline to nadir platelet count are shown in [Figure 15](#) and [Figure 16](#) for CS3 and CS8, respectively, allowing one to note the proportion of patients in each arm of each trial that had a percent reduction in platelets of any amount of interest (or greater). For example, it can be easily discerned that ~50% of patients assigned to olezarsen in CS3 had $\geq 30\%$ reduction in platelet count from baseline to on-study nadir.

Figure 15. Cumulative Distribution Functions for Percent Change From Baseline to Platelet Count Nadir, Trial CS3



Source: Applicant response to Division IR, NDA 218614, SDN 14, July 24, 2024

Figure 16. Cumulative Distribution Functions for Percent Change From Baseline to Platelet Count Nadir, Trial CS8



Source: Applicant response to Division IR, NDA 218614, SDN 14, July 24, 2024

Categorical changes in platelet values at any time postbaseline are described in [Table 68](#) for subjects in CS3 and CS8.

No olezarsen-treated subject experienced a platelet count $<50 \times 10^9/L$. There was one placebo-treated subject with a platelet count $<25 \times 10^9/L$, however, a local laboratory result on the same day was $>140 \times 10^9/L$. The outlier result was likely the result of a delay in sample analysis of almost 1 month by the central laboratory.

Table 68. Number (%) of Subjects With Nadir Platelet Values ($10^9/L$) Meeting Threshold Value or Percent Reduction at Any Time Postbaseline: Trials CS3, CS8, and CS13-OLE Treatment-Naïve

	CS3			CS8			CS13
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)	OLZ Treatment-Naïve N=20 n (%)
Any occurrence	6 (28.6)	5 (22.7)	5 (21.7)	0	3 (5.3)	1 (2.6)	3 (15.0)
Nadir platelet count postbaseline							
100 to <140	5 (23.8)	9 (40.9)	3 (13.0)	10 (17.2)	7 (12.3)	0	3 (15.0)
75 to <100	5 (23.8)	3 (13.6)	3 (13.0)	0	3 (5.3)	0	2 (10.0)
50 to <75	1 (4.8)	2 (9.1)	1 (4.3)	0	0	1 (2.6)	1 (5.0)
25 to <50	0	0	0	0	0	0	0
<25	0	0	1 (4.3)	0	0	0	0
$\geq 30\%$ decrease from baseline	9 (42.9)	11 (50.0)	7 (30.4)	12 (20.7)	14 (24.6)	2 (5.1)	11 (55.0)
$\geq 50\%$ decrease from baseline	2 (9.5)	2 (9.1)	3 (13.0)	1 (1.7)	3 (5.3)	1 (2.6)	2 (10.0)

Note: Subjects with more than one value were counted once under the worst category. Both local and central laboratory results were used.

Source: CS3 CSR Table 46; CS8 CSR Table 45; CS13 CSR Table 39; CDS Reports
Abbreviations: OLZ, olezarsen; PBO, placebo

Adverse Events Related to Platelet Count or Bleeding Events

Reduced Platelet Count Event Terms

In CS3 and CS8, a higher proportion of olezarsen-treated compared to placebo-treated subjects had AEs reported related to a reduced platelet count. Not all cases of thrombocytopenia or platelet count reductions were reported as AEs, and it is unclear whether investigators employed a systematic approach to determining whether a reduction in platelet count qualified as an “adverse event” and whether such an event should be reported as a decrease in platelet count or thrombocytopenia. Therefore, the number of events portrayed in [Table 69](#) is lower than the actual number of cases that occurred in the trials, and a distinction between the event terms should not be overinterpreted. In CS3 and CS8, no subjects discontinued due to a thrombocytopenia-related AE.

Table 69. Treatment-Emergent Adverse Events Related to Reduced Platelet Count Terms, Trials CS3 and CS8

Adverse Event	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
≥1 treatment-emergent thrombocytopenia AE	2 (9.5)	3 (13.6)	1 (4.3)	0	2 (3.5)	0
Platelet count decreased	1 (4.8)	3 (13.6)	1 (4.3)	0	1 (1.8)	0
Thrombocytopenia	1 (4.8)	0	0	0	1 (1.8)	0

Source: CS3 CSR, Table 45; CS8 CSR, Table 44 Confirmed by CDS Report
Abbreviations: AE, adverse event; OLZ, olezarsen; PBO, placebo

Bleeding Event Terms

Bleeding events were tabulated below using the MedDRA Hemorrhage SMQ. SMQs are validated sets of MedDRA terms used to investigate specific safety topics. The Hemorrhage SMQ includes preferred terms that refer not only to clinical bleeding events but also to abnormal laboratory values (e.g., decreased hemoglobin), which may or may not be caused by bleeding. Additional analyses were done to exclude events at the injection site and/or related to a laboratory value, as well as evaluation of events in subjects with concomitant anticoagulant or antiplatelet medications.

Using the Hemorrhage SMQ, the proportion of subjects with an event was similar across treatment groups in Trials CS3 and CS8. After excluding events that were localized to the injection site or represent a laboratory value, there was no meaningful differences were noted in “clinical” bleeding events across treatment groups.

No olezarsen-treated subject in Trial CS3 paused, reduced, or discontinued olezarsen dosing due to a bleeding TEAE. Most of the subjects in Trial CS3 were not on concomitant anticoagulant or antiplatelet medications at the time of a clinical bleeding event. In contrast, with the exception of the clinical bleeding TEAE of epistaxis in a subject in the olezarsen 80 mg group, all “clinical” bleeding TEAEs in Trial CS8 were experienced by subjects concomitantly receiving anticoagulant or antiplatelet medications in Trial CS8. There were three olezarsen-treated subjects in Trial CS8 who discontinued, paused, or reduced study medication due to a bleeding AE at the injection site – ‘injection site bruising’ (n=1); ‘injection site hemorrhage’ (n=2) - none

were serious. In CS13, there was one SAE of bleeding, ‘lower gastrointestinal hemorrhage’ in a treatment-naïve subject while taking 80 mg olezarsen. In CS7, there was a serious bleeding TEAE of ‘hematemesis’. Summaries of the SAEs due to bleeding TEAEs in subjects taking olezarsen follow [Table 70](#).

Table 70. Bleeding Events – Hemorrhage SMQ, Trials CS3, CS8, and CS13

Adverse Event	CS3			CS8			CS13
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)	OLZ Treatment- Naïve N=20 n (%)
Hemorrhage SMQ TEAE	3 (14.3)	4 (18.2)	4 (17.4)	3 (5.2)	3 (5.3)	2 (5.1)	3 (15.0)
Clinical Bleeding AE*	3 (14.3)	2 (9.1)	3 (13.0)	1 (1.7)	2 (3.5)	2 (5.1)	2 (10.0)
Epistaxis*	2 (9.5)	0	1 (4.3)	0	1 (1.8)	0	0
Contusion*	1 (4.8)	1 (4.5)	0	0	0	1 (2.6)	0
Hematochezia*	0	1 (4.5)	0	0	0	0	0
Gastric varices hemorrhage*	0	0	1 (4.3)	0	0	0	0
Hematemesis*	0	0	1 (4.3)	0	0	0	0
Hematuria*	0	0	0	0	1 (1.8)	0	0
Bone contusion*	0	0	0	1 (1.7)	0	0	0
Eye contusion*	0	0	0	0	0	1 (2.6)	0
Hematoma*	0	0	0	0	0	1 (2.6)	0
Lower gastrointestinal hemorrhage*	0	0	0	0	0	0	1 (5.0)
Hemorrhoidal hemorrhage*	0	0	0	0	0	0	1 (5.0)
Injection site bruising	0	1 (4.5)	0	0	1 (1.8)	0	0
Injection site hemorrhage	0	0	0	2 (3.4)	0	0	0
Injection site hematoma	0	0	0	0	0	0	1 (5.0)
Hemoglobin decreased	0	1 (4.5)	1 (4.3)	0	0	0	0
Hematocrit decreased	0	1 (4.5)	0	0	0	0	0
INR increased	0	0	0	0	0	1 (2.6)	0

Source: CS3 Table 14.3.2.10.1, CS3 CSR Table 43; CS8 CSR Table 42

*Clinical bleeding AE defined as events identified based on the Hemorrhage MedDRA, but excludes events at the injection site and events related to a laboratory value

Abbreviations: AE, adverse event; CSR, clinical study report; INR, international normalized ratio; MedDRA, Medical Dictionary for Regulatory Activities; OLZ, olezarsen; PBO, placebo; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event

- Subject ID (b) (6) (CS3/CS13) – ‘lower gastrointestinal hemorrhage’ - 32-year-old male with FCS and history of pancreatitis, initially enrolled in index Trial CS3 (assigned to placebo) and then continued in Trial CS13. After rolling over to CS13, but prior to the first dose of olezarsen 80 mg, the patient experienced SAEs of pancreatitis necrotizing, cholangitis, and pancreatogenous diabetes which required hospitalization, and placement of biliary stents. The subject recovered and began receiving olezarsen 80 mg Q4W. On Study Day 44 of CS13, the subject experienced cholangitis secondary to an abdominal drain installation. The subject was on the anticoagulant dalteparin during this time due to bile duct stent placement. The subject received a dose of olezarsen on Day 57. On Study Day 71, the subject presented to the emergency department due to two dark stools. The patient experienced both a serious TEAE of lower gastrointestinal hemorrhage and anemia related to the gastrointestinal hemorrhage. Laboratory values noted anemia (hemoglobin 6.8 g/dL reference range 14.0-18.0) and platelet count of 431 x 10⁹/L. The subject was subsequently

hospitalized, anticoagulant therapy stopped (narrative states dalteparin and warfarin stopped), and blood transfusion was received. Gastroscopy revealed the presence of small esophageal varices without red signs. However, near the anastomosis, there was a presence of edematous mucosa, which had very tortuous folds and there were indelible clots in one of the folds. An echo-endoscopy was conducted to clarify the origin of the clot, and the result revealed no gastric varices. Hemoglobin on Day 75 was 8.0 g/dL. While hospitalized the subject experienced an adjudicated case of mild pancreatitis. The subject was discharged on Study Day 76. He continued to receive olezarsen. In the 90-day safety update, it was noted that the subject's platelet count during the OLE fell to $68 \times 10^9/L$ on OLE Study Day 421/Week 61. A gross hemolysis was noted for the patient's blood sample. Laboratory tests were repeated on the same day (OLE Study Day 421) which showed platelet counts of $151 \times 10^9/L$ (central lab) and $127 \times 10^9/L$ (local lab). Subsequent platelet count on OLE Study Day 449 (Week 65) was $142 \times 10^9/L$. No concurrent bleeding TEAE was reported and the treatment with the Study Drug continued without interruption. No other platelet counts of $<140 \times 10^9/L$ were observed for this patient during the study.

Reviewer Comment

This subject had persistent complications secondary to necrotizing pancreatitis and biliary disease which began during placebo treatment in CS3 requiring abdominal drains and anticoagulant therapy which may have contributed to this subject's lower gastrointestinal bleed and resulting anemia. This subject had low levels of hemoglobin prior to this event and during placebo treatment in Trial CS3 (Day 383 of CS3/ Day -35 from first olezarsen dose: hemoglobin 9.0 g/dL, Day 39 post-olezarsen hemoglobin of 8.4 g/dL). The subject has continued with olezarsen treatment – hemoglobin levels are below normal (Day 295, hemoglobin 10.1 g/dL) but no additional bleeding events have been reported. Platelet count fell 50% from baseline but had remained within normal limits, apart from one sample that had hemolysis and did not have a confirmed low value with repeat testing on the same day.

- Subject ID # (b) (6) (CS7) - 'hematemesis' 50-year-old female with FCS previously treated with volanesorsen for approximately 2.5 years, enrolled in the open-label study, CS7 and received olezarsen 80 mg Q4W. At the qualification visit, hemoglobin was 11.9 g/dL (12.0-16.0 g/dL), platelet count was $205 \times 10^9/L$. On Study Day 155, the subject was hospitalized due to abdominal pain, bloody vomiting (~30 to 40 times), and diarrhea, but no melena. Abnormal test results included: MCV of 78 fL, red blood cells of $5.37 \times 10^{12}/L$, RDW of 19.5%, protein of 87 g/L, ALT of 103 U/L, AST of 95 U/L, gamma-glutamyl transferase (GGT) of 41 U/L, and high sensitivity C-reactive protein of 9.3 mg/L (no reference ranges, hemoglobin, or platelet count provided). On Day 162, hemoglobin was 10.7 g/dL and platelet levels were within reference range. The primary diagnosis was hematemesis, possibly secondary to a Mallory-Weiss tear from vomiting. The Pancreatitis Adjudication Committee did not adjudicate this event as pancreatitis. The subject was discharged from the hospital and considered recovered on Day 162. No action was taken with olezarsen, and the subject continued to receive olezarsen.

Reviewer Comment

This reviewer concurs with the assessment that hematemesis most likely due to persistent vomiting and unlikely to be related to olezarsen treatment.

Conclusion

Olezarsen treatment causes reductions in platelet count but there is no evidence of an increased clinical risk of bleeding. The decrease in platelet count occurs within the first weeks of treatment and is characterized by a gradual decline over time. Platelet counts tend to remain on average 5 to 15% below baseline. Overall, the proportion of subjects experiencing a clinical bleeding AE, defined as those not occurring at the injection site or associated with a laboratory term, were similar across treatment groups. No olezarsen-treated subjects, to date, have reported a platelet count below $50 \times 10^9/L$. There were two serious clinical bleeding events in olezarsen-treated subjects in the OLE studies, CS13 and CS7. Although temporally associated with olezarsen treatment, it is this reviewer's assessment that concomitant medications and/or underlying comorbidities offer a plausible alternate etiology, especially given continued treatment with olezarsen in these two subjects without further bleeding events.

7.7.3. Increases in Liver Enzymes

Issue

Serious hepatic AEs in subjects treated with olezarsen were observed. Mean increases in liver enzymes associated with olezarsen treatment and cases of categorical increases in liver enzymes greater than the ULN in olezarsen-treated subjects were also observed.

Background

Risk of hepatotoxicity with elevation of ALT and AST and hepatic steatosis has been indicated in mipomersen and inotersen, which are ASOs targeting hepatic gene expression. Inotersen labeling recommends baseline and monthly monitoring of liver enzymes ([Severi et al. 2023](#); [Akcea Therapeutics 2024a](#)). Vupanorsen, an ASO targeting ANGPTL3, which is a key regulator in TG metabolism, caused a dose-dependent increase in hepatic fat fraction ([Zimmerman et al. 2024](#)). In contrast, volanesorsen, in clinical trials of different patient populations of HTG including FCS, reduced hepatic fat fraction by 24 to 53% placebo-corrected from baseline ([Prohaska et al. 2023](#)). Olezarsen includes the Gal-NAc receptor which targets it to the liver, its therapeutic site for its mechanism of action. The olezarsen clinical development program for the FCS treatment indication did not include assessments of hepatic fat.

Assessment

Adverse Events

TEAEs related to abnormal hepatic function were evaluated by the following queries – Drug Related Hepatic Disorders Comprehensive Search SMQ (narrow and broad), Hepatic Injury FMQ (narrow) and Hepatic Failure FMQ (narrow), and review of the hepatobiliary and investigations SOC. There were no events related to Hepatic Failure FMQ (narrow) in any of the trials (including the open-label extension studies). The Hepatic Injury FMQ and Drug Related Hepatic Disorders SMQ, yielded similar results given the significant overlap between the terms comprising each query. [Table 71](#) lists the adverse terms related to hepatic function in Trials CS3 and CS8.

There was one SAE of ‘hepatic cirrhosis’ in an olezarsen-treated subject and two SAEs, ‘gastric varices’ and ‘gastric varices hemorrhage’, in a placebo-treated subject in Trial CS3. One SAE of ‘cholangitis’ was reported in an olezarsen-treated subject in CS13. The subject with cholangitis has been discussed previously ([Subject ID \(b\) \(6\)](#)) in the context of an SAE of lower gastrointestinal hemorrhage. Cholangitis appeared secondary to complications related to pancreatitis and subsequent biliary stents and drains.

Two olezarsen-treated subjects (CS8- (b) (6); CS8- (b) (6)) in CS8 discontinued treatment due to a hepatic-related AE ‘liver function enzyme increased’ and ‘ALT increased’. There were additional subjects that had their study drug interrupted in CS8 due to liver enzyme increases. There were no hepatic-related SAEs in CS8. Brief summaries of the SAE of ‘cirrhosis’ and discontinuations due to AE are summarized below.

Table 71. Hepatic-Related Treatment-Emergent Adverse Events, Trials CS3 and CS8

	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
Abnormal Liver Function						
TEAE	1 (4.8)	2 (9.1)	3 (13.0)	7 (12.1)	5 (8.8)	2 (5.1)
SAE	0	1 (4.3)	1 (4.3)	0	0	0
DAE	0	0	0	2 (3.4)	0	0
ALT increased ^a	0	1 (4.5)	1 (4.3)	3 (5.2)*	3 (5.3)	0
AST increased ^a	0	1 (4.5)	1 (4.3)	1 (1.7)	1 (1.8)	0
GGT increased ^b	1 (4.3)	1 (4.5)	1 (4.3)	2 (3.4)	2 (3.5)	0
Gastric varices ^a	0	0	1 (4.3)#	0	0	0
Gastric varices hemorrhage ^a	0	0	1 (4.3)#	0	0	0
Hepatic cirrhosis ^a	0	1 (4.5)#	0	0	0	0
Hepatosplenomegaly ^a	0	1 (4.5)	0	0	0	0
Non-alcoholic fatty liver ^a	0	1 (4.5)	0	0	0	0
Esophageal varices ^a	0	1 (4.5)	0	0	0	0
Non-alcoholic steatohepatitis ^a	0	0	0	1 (1.7)	0	0
Hepatomegaly ^a	0	0	0	0	0	1 (2.6)
Liver function test increased ^b	0	0	0	3 (5.2)*	1 (1.8)	0
Blood alkaline phosphatase increased ^b	0	0	0	0	1 (1.8)	0
INR increased ^b	0	0	0	0	0	1 (2.6)

Source: CS3 CSR Table 53; CS8 CSR Table 53; CS13, CSR Table 42; CS7, CSR Table 14.3.1.2

^a Reported in both Drug-Related Hepatic Disorders Comprehensive SMQ (broad and narrow) and Hepatic Injury FMQ (narrow).

^b Reported in Drug-Related Hepatic Disorders Comprehensive SMQ (broad and narrow) only

^c Reported in the hepatobiliary SOC

#Serious AE; * Discontinuation due to AE

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAE, discontinuation due to AE; FMQ, FDA Medical Query; GGT, gamma-glutamyltransferase; SAE, serious adverse event; SMQ, SOC, system organ class; TEAE, treatment-emergent adverse event

- Subject # (b) (6) Trial CS3 ‘cirrhosis’ SAE: 71-year-old man with FCS previously treated with volanesorsen for 2 years (last dose (b) (6)), with a history of hepatic steatosis ((b) (6)) randomized to treatment of 80 mg olezarsen experienced TEAE of hepatic cirrhosis on Study Day 295 after the 10th dose of olezarsen (Week 41). At the Week 45 (Study Day 323) study visit, the subject complained about progressive worsening of abdominal distension with increasing shortness of breath, and lower extremity swelling. The subject reported “dealing with edema and abdominal distension over the past year”. The subject was

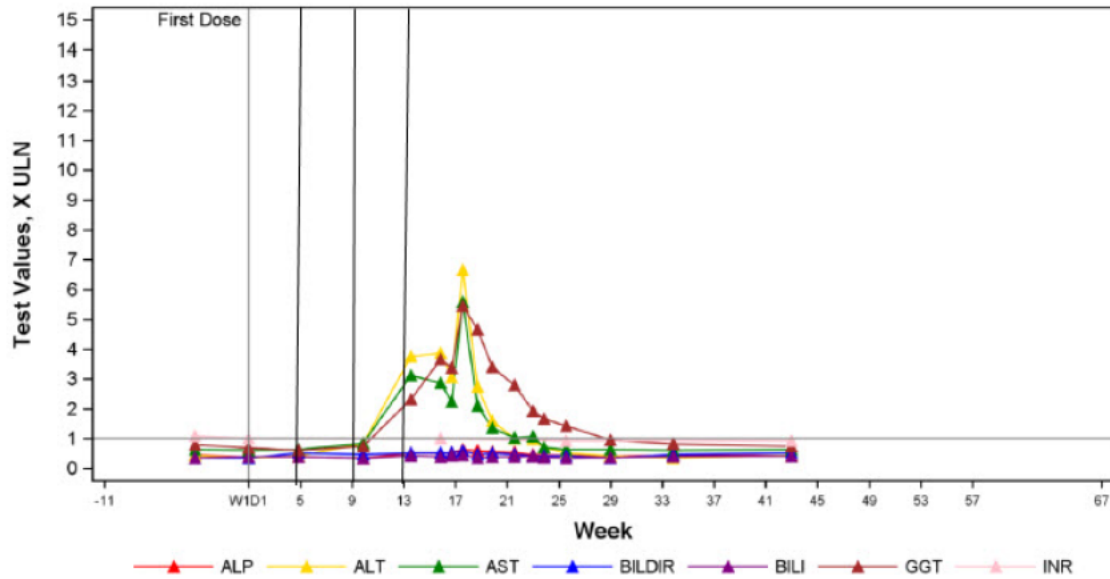
sent to the Emergency Department; the subject was considered hemodynamically stable. CT of abdomen was notable for portal hypertension, varices, and liver cirrhosis (SAE hepatic cirrhosis), and 5.5 L of ascites was removed. The subject's laboratory value for ALT was 26 U/L and AST was 52 (reference range <50 U/L). Total bilirubin and international normalized ratio (INR) values were slightly above normal 1.7 mg/dL (reference range 0.2-1.3 mg/dL), and 1.7 (reference range 0.8-1.1), respectively. Hemoglobin and platelet count values were below normal at 10.7 g/dL (reference range 14-18 g/dL) and $106 \times 10^9/L$ (reference range $150-400 \times 10^9/L$). Upper gastrointestinal (GI) endoscopy noted esophageal varices and four bands were placed to deflate the varices. The subject was discharged from the hospital the next day. The subject continued to take olezarsen and is currently enrolled in CS13. ALT and AST remain in normal range. Direct bilirubin levels have ranged mostly within the normal range – no values have been 2x above the ULN.

Reviewer Comment

Underlying comorbidity of hepatic steatosis confounds an assessment of causality with olezarsen.

- Subject #CS8-(b) (6) Trial CS8 'liver function test increased' DAE: 73-year-old woman with HTG at risk for ASCVD, who was randomized to olezarsen 50 mg Q4W. Baseline ALT and AST were 23 U/L and 27 U/L, respectively (reference range ALT 10-53 U/L; AST 14-43 U/L) On Study Day 89, the subject received her 4th dose of olezarsen. Laboratory values on that day were notable for ALT and AST >3x ULN (ALT 199 U/L, AST 134 U/L) leading to an AE of 'liver function test increased'. On Study Day 94 she reported 'fatigue'. As a result of these events, study drug administration was paused per stopping rules for elevated liver enzymes and symptoms, and ultimately led to the subject permanently discontinuing study drug. The subject's ALT and AST peaked at 352 U/L and 240 U/L on Study Day 117, respectively. Bilirubin and alkaline phosphatase remained within normal limits. The ALT and AST returned toward normal range over the next 2 months while off study drug. The last laboratory values for ALT and AST were 53 U/L and 44 U/L on Study Day 145.

Figure 17. Subject (b) (6) -Olezarsen 50 mg - Elevated Liver Enzymes, Trial CS8



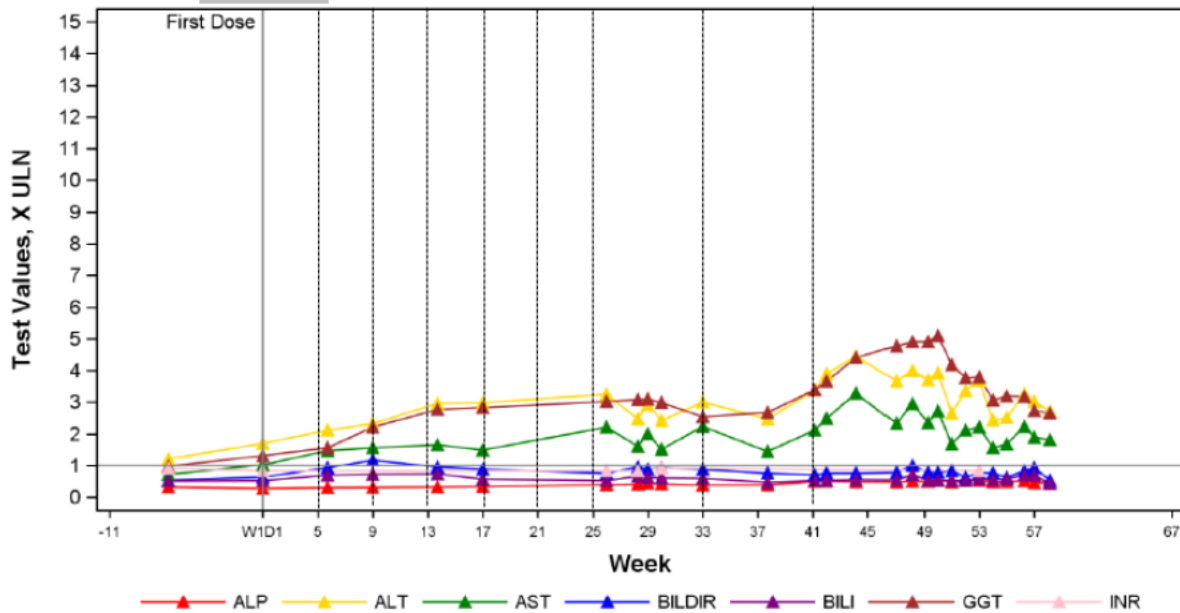
Source: CS8 CSR, Figure 45

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILDIR, direct bilirubin; BILI, bilirubin; GGT, gamma-glutamyltransferase; INR, international normalized ratio; ULN, upper limit of normal

Reviewer Comment

Causal association with olezarsen cannot be ruled out given the temporal association with olezarsen treatment and positive dechallenge.

- Subject #CS8-(b) (6), CS8 drug interruption and DAE; 'elevated ALT', 50 mg olezarsen: 55-year-old man randomized to 50 mg olezarsen with ALT elevation $\geq 3x$ ULN on Study Day 176 (Week 25). Baseline values were notable for an elevated ALT at baseline of 90 U/L (reference range 10 to 53 U/L) and GGT of 68 U/L (reference range 11 to 52 U/L). All other liver enzyme values were within the reference range. On Study Day 176 (Week 25), the subject's ALT was 172 U/L and AST of 95 U/L. Study drug was interrupted until Week 33. Treatment resumed until Week 41, when subject experienced another ALT elevation $\geq 3x$ ULN (ALT 179 U/L and AST 91 U/L). Study drug was interrupted again. ALT and AST remained elevated but were trending towards baseline. Treatment did not restart by the time the study ended.

Figure 18. Subject (b) (6) –Olezarsen 50 mg – Elevated Liver Enzymes, Trial CS8

Source: CS8 CSR, Figure 46

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILDIR, direct bilirubin; BILI, bilirubin; GGT, gamma-glutamyltransferase; INR, international normalized ratio; ULN, upper limit of normal

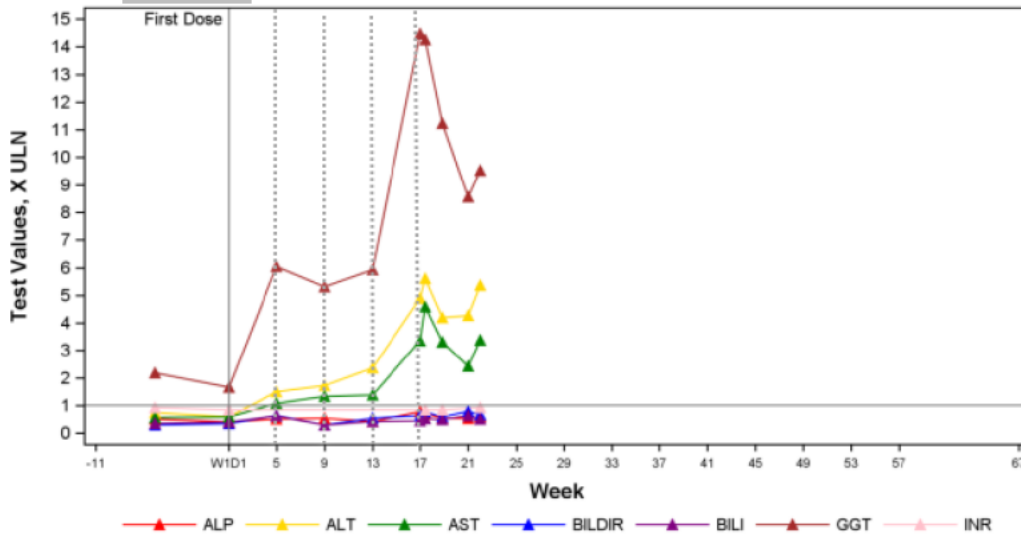
Reviewer Comment

This subject was considered on a drug interruption at the end of the study but was coded as a discontinuation due to an AE in adsl.xpt. Note in the adae.xpt dataset this subject is not listed as discontinuing due to an AE. This reviewer concurs with the adsl.xpt dataset characterization of disposition for this subject as discontinuation due to an AE.

- CS8-(b) (6): 44-year-old male patient experienced ALT and AST elevations $\geq 3 \times$ ULN on Study Day 113, following the Week 17 dose of study drug administered on the same day. On Study Day 1, the patient's liver function test results were as follows: ALT of 31 U/L (reference range: 10 to 53 U/L), AST of 25 U/L (reference range: 14 to 43 U/L), alkaline phosphatase of 59 U/L (reference range: 41 to 146 U/L), total bilirubin of 8.2 μ mol/L (reference range: 4.3 to 20.7 μ mol/L), INR of 1.0 (reference range: 0.8 to 1.2), and GGT of 86 U/L (reference range: 11 to 52 U/L). On Study Day 29 (Week 5), the patient experienced a non-serious, TEAE of non-alcoholic steatohepatitis (mild) that was ongoing through the remainder of the study; the TEAE was assessed as unlikely related to study drug. On Study Day 113, the patient's ALT and AST levels were 259 U/L (reference range: 10 to 53 U/L) and 144 U/L (reference range: 14 to 43 U/L), respectively. Study Day 116 was the peak ALT and AST values during the study, which were 297 U/L ($\geq 5 \times$ ULN) and 197 U/L, respectively, after which ALT and AST levels generally remained $\geq 3 \times$ ULN through Study Day 148 (with an exception of AST levels at Study Day 141 [Week 21], which were $\geq$ ULN, but $< 3 \times$ ULN [actual value 104 U/L]), the last day that data are available for this patient. These elevations were not reported as TEAEs. The patient also had elevated GGT levels $\geq 3 \times$ ULN starting on Study Day 29 (314 U/L) and continuing through the Study Day 148 (ranging from 276 U/L to 752 U/L, with a peak on Study Day 113). Study drug was interrupted after study drug administration on Study Day 113, and weekly monitoring was

initiated on Study Day 141 (Week 21); the patient did not resume study drug following study drug interruption. The patient terminated the study early at Study Day 218 (the patient was lost to follow-up). No data are available in the period from Study Day 148 to Study Day 218. A plot showing relevant liver function parameters over time for this patient is presented in [Figure 19](#) below.

Figure 19. Subject (b) (6) –Olezarsen 50 mg – Elevated Liver Enzymes, Trial CS8



Source: [Figure 14.3.4.1.3](#)

Note 1: Includes patients with at least 3-fold or greater elevations above the ULN for ALT or AST or patients with baseline ALT or AST $\geq$ ULN and at least 2-fold increases from Baseline.

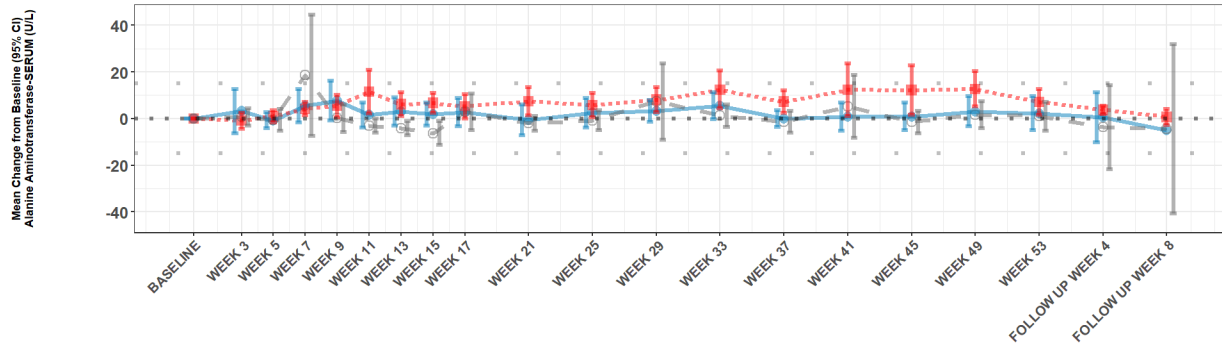
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILDIR = Direct Bilirubin; BILI = total bilirubin; INR = international normalized ratio; GGT = gamma-glutamyltransferase; ULN = upper limit of normal; W1D1 = Week 1, Day 1

Source: CS8 CSR Figure 14.3.4.1.3

Mean Changes in Liver Enzymes

Mean changes from baseline were larger in the olezarsen treatment group but remained within normal reference ranges.

Figure 20. Mean Laboratory (Liver Biochemistry) Data Change From Baseline Over Time, Safety Population, Trial ISIS-678354-CS3

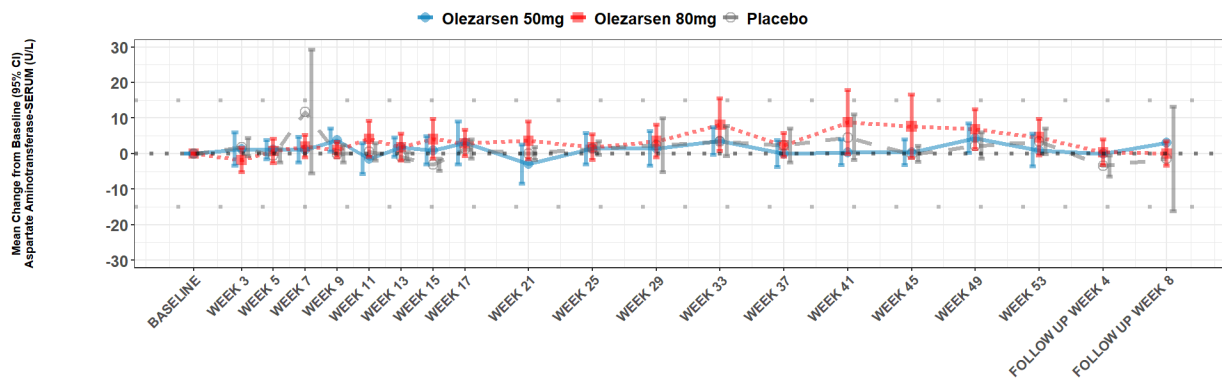


Mean Change from Baseline / Mean Value

Olezarsen 50mg	0/19	3.1023	-0.7918	5.4265	7.5268	1.5222	3/23	1.8222	2.7031	-0.5321	2.5203	3.2204	5.4265	-0.0620	0.6521	0.8921	3.1023	2.2223	0.5112	-5/12
Olezarsen 80mg	0/23	-0.9523	0.9523	4.2265	5.4265	12/32	6.1228	6.7229	5.2228	7.4230	5.8229	8.1031	12/05	7.2200	12/05	12/05	13/05	7.2200	3.7115	0.6712
Placebo	0/24	0.7124	-0.6822	19/43	0.1824	-3/21	-4.3220	-6.3220	2.9228	-2/22	-0.7523	7.2232	1.3226	-1.5223	5.1229	-1.5221	1.5226	0.9525	-3.7223	-4.5200

Number of Patients with Both Baseline and Post-baseline Data

Olezarsen 50mg	21	20	19	20	19	18	20	18	19	17	19	18	18	17	19	19	18	2	1	
Olezarsen 80mg	22	19	20	18	19	18	20	20	19	20	19	19	19	19	19	19	19	3	3	
Placebo	23	21	22	22	22	22	22	18	21	22	20	21	21	22	22	19	22	21	3	2



Mean Change from Baseline / Mean Value

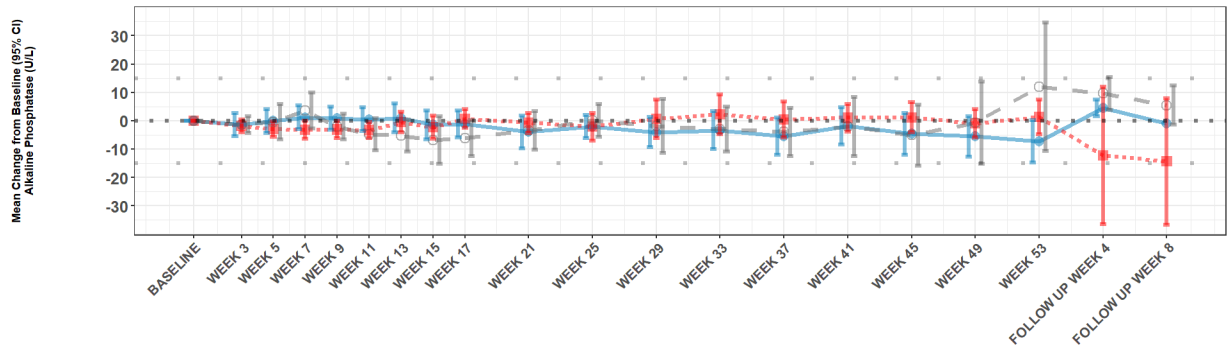
Olezarsen 50mg	0/21	1.2223	1/21	1.1223	3.8226	-1.5221	1.8222	0.8823	2.9225	-3/20	1.3223	1.4224	3.5224	-0.0622	0.2523	0.2822	4.2226	0.9424	0/15	3/18
Olezarsen 80mg	0/26	-1.8224	0.7427	2/27	1.1225	-4.1228	1.8227	4/30	2.9228	3.6229	1.8228	3.5229	8.1034	2.4228	8.8035	7.6033	6.8033	4.6030	0.3317	0/17
Placebo	0/23	1.8225	-0.5523	12/36	-0.1423	0.4524	-1/23	-3.2223	1.2225	-0.1223	1.5224	2.4227	3.5227	2.2226	4.5228	-0.1624	2.2226	3.4227	-3.5222	-1.5224

Number of Patients with Both Baseline and Post-baseline Data

Olezarsen 50mg	20	19	18	18	16	16	18	16	18	14	18	15	17	17	16	18	17	16	1	1
Olezarsen 80mg	22	19	19	18	17	18	20	20	19	19	19	19	19	19	19	19	19	18	3	3
Placebo	23	19	20	21	22	22	21	16	20	20	20	20	20	21	22	19	21	19	2	2

NDA 218614
Tryngolza (olezarsen sodium)

(Figure 20 continued)

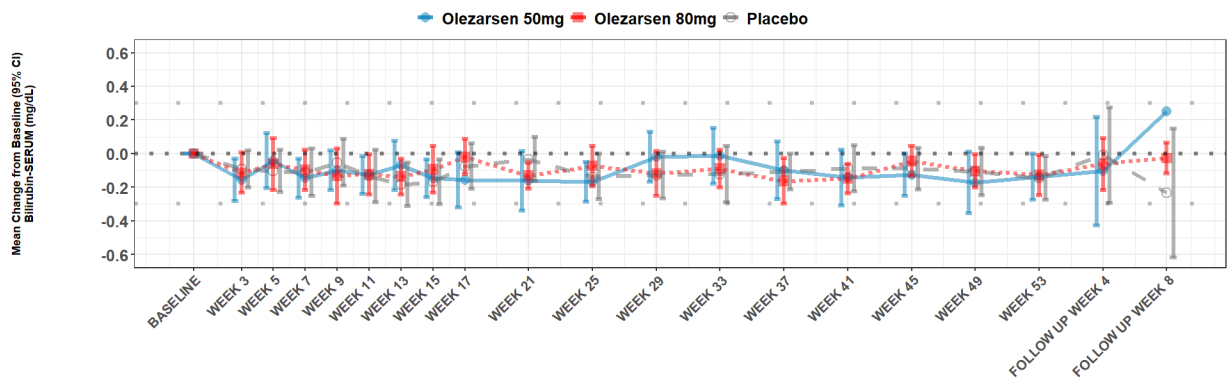


Mean Change from Baseline / Mean Value

Olezarsen 50mg	0.70	-1.458	-0.1569	1.172	0.8471	0.569	0.972	-1.468	-1.272	-4.69	-2.271	-4.168	-3.369	-5.466	-1.970	-4.768	-5.667	-7.366	4.538	-136
Olezarsen 80mg	0.54	-1.852	-3.52	-3.151	-3.152	-3.351	-0.4554	-2.352	0.755	-0.854	-2.251	0.6854	2.357	0.4754	1.65	1.155	-0.8953	1.355	-1248	-1446
Placebo	0.53	-1.462	-0.4363	3.767	-2.63	-4.760	-5.260	-8.859	-6.160	-3.562	0.159	-1.893	-3.62	-4.59	-2.161	-5.158	-0.7362	1274	9.757	5.556

Number of Patients with Both Baseline and Post-baseline Data

Olezarsen 50mg	21	20	20	20	19	18	20	18	19	17	19	18	18	18	17	19	19	18	2	1
Olezarsen 80mg	22	19	20	20	19	18	20	20	20	20	19	19	18	19	19	19	19	19	3	3
Placebo	23	23	23	22	22	22	22	18	21	22	21	21	21	22	22	19	22	21	3	2



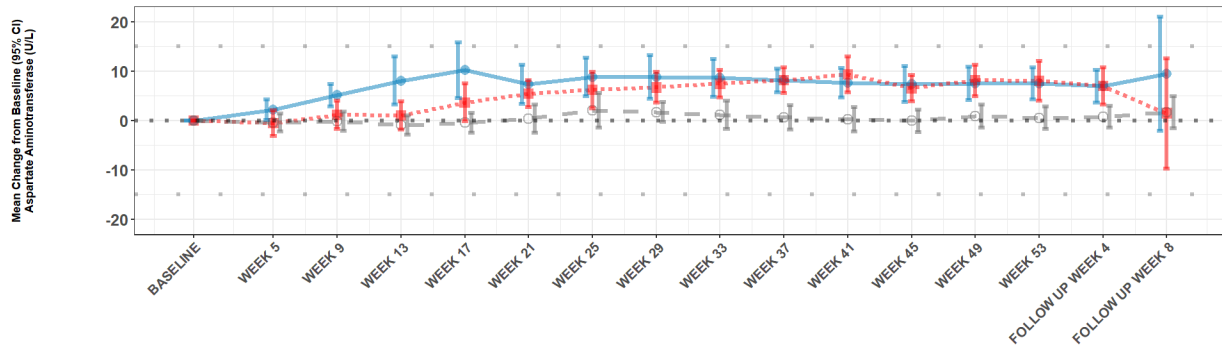
Mean Change from Baseline / Mean Value

Olezarsen 50mg	0.0.69	-0.160.550.040.660.150.55	-0.10.6	-0.130.590.070.620.150.570.160.53	-0.160.53	-0.170.52	-0.020.65	-0.010.68	-0.10.6	-0.140.57	-0.130.56	-0.170.52	-0.140.57	-0.10.6	0.250.68		
Olezarsen 80mg	0.0.68	-0.110.590.060.64	-0.10.6	-0.130.570.120.530.140.55	-0.090.6	0.020.68	-0.130.57	-0.070.63	-0.120.59	-0.090.63	-0.160.54	-0.150.56	-0.040.66	-0.110.6	-0.130.58	-0.060.61	-0.030.55
Placebo	0.0.69	-0.090.59	-0.10.58	-0.110.580.050.630.130.55	-0.180.5	-0.170.540.080.62	-0.030.65	-0.140.57	-0.130.56	-0.120.56	-0.110.58	-0.090.6	-0.090.61	-0.110.58	-0.150.53	-0.010.57	-0.230.38

Number of Patients with Both Baseline and Post-baseline Data

Olezarsen 50mg	21	20	20	20	19	18	20	18	19	17	19	18	18	18	17	19	19	18	2	1
Olezarsen 80mg	22	20	20	20	19	18	20	20	20	20	19	19	18	19	19	19	19	19	3	3
Placebo	23	23	23	22	22	22	22	18	21	22	21	21	21	22	22	19	22	21	3	2

(Figure 21 continued)

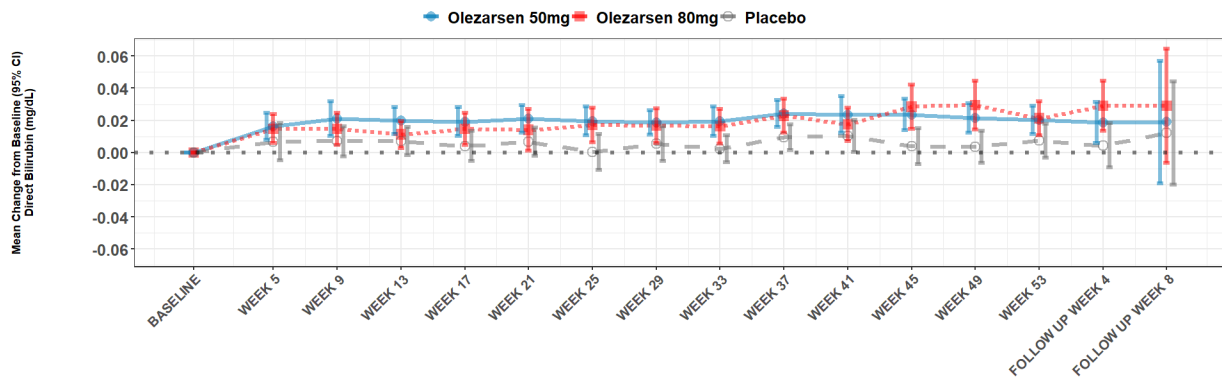


Mean Change from Baseline / Mean Value

Olezarsen 50mg	0.021	2.1/23	5.1/26	8.1/29	10/31	7.3/27	8.8/30	8.8/29	8.7/29	8.1/29	7.6/28	7.4/28	7.5/28	7.5/28	6.9/29	9.4/36
Olezarsen 80mg	0.022	-0.53/21	1.1/23	1/23	3.7/26	5.4/27	6.2/27	6.7/28	7.5/29	8.1/29	9.3/31	6.5/28	8.1/29	8/29	7/28	1.5/27
Placebo	0/18	-0.37/18	-0.15/18	-0.97/17	-0.44/18	0.33/18	2/20	1.7/20	1.2/19	0.62/18	0.29/18	-0.98/18	0.69/19	0.55/19	0.7/18	1.7/21

Number of Patients with Both Baseline and Post-baseline Data

Olezarsen 50mg	58	57	53	53	53	52	51	47	45	47	47	46	47	47	29	9
Olezarsen 80mg	57	57	57	56	52	49	51	49	50	49	48	46	50	49	35	11
Placebo	39	38	39	38	39	39	37	36	38	37	38	36	37	38	23	9



Mean Change from Baseline / Mean Value

Olezarsen 50mg	0.0/0.0	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/11
Olezarsen 80mg	0.0/1	0.010/11	0.010/11	0.010/11	0.010/11	0.010/11	0.020/11	0.020/11	0.020/11	0.020/11	0.020/12	0.020/12	0.030/13	0.030/13	0.020/12	0.030/12
Placebo	0.0/0.0	0.010/1	0.010/1	0.010/1	0.0/1	0.010/1	0.0/0.0	0.010/1	0.0/1	0.010/1	0.010/1	0.0/0.0	0.0/0.0	0.010/1	0.0/1	0.010/11

Number of Patients with Both Baseline and Post-baseline Data

Olezarsen 50mg	58	57	53	53	53	52	51	47	45	47	47	46	47	47	29	9
Olezarsen 80mg	57	57	57	56	52	49	51	49	50	49	48	46	50	49	35	11
Placebo	39	38	39	38	39	39	37	36	38	37	38	36	37	38	23	9

Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Only central laboratory data are included in the analysis.
 Abbreviations: CI, confidence interval

Categorical Changes in Liver Enzymes

In CS3, CS13, and CS7 no olezarsen-treated subjects experienced ALT elevations $\geq 3x$ ULN or $\geq 5x$ ULN. There was one olezarsen-treated subject in CS3 with drug interruption due to abnormal liver function test results (AST and GGT $\geq 3x$ ULN, ALT $>ULN$ but $<3x$ ULN) (CS3-(b) (6)).

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In CS8, there were more olezarsen-treated subjects with categorical elevations in ALT and AST than placebo-treated subjects.

There were no cases of Hy's Law defined as peak total bilirubin >2x ULN and peak ALT or AST >3x ULN in any trial.

GGT was the most commonly reported elevated liver enzyme. Increases occurred in a higher proportion of olezarsen-treated subjects. The significance of this increase in GGT is uncertain.

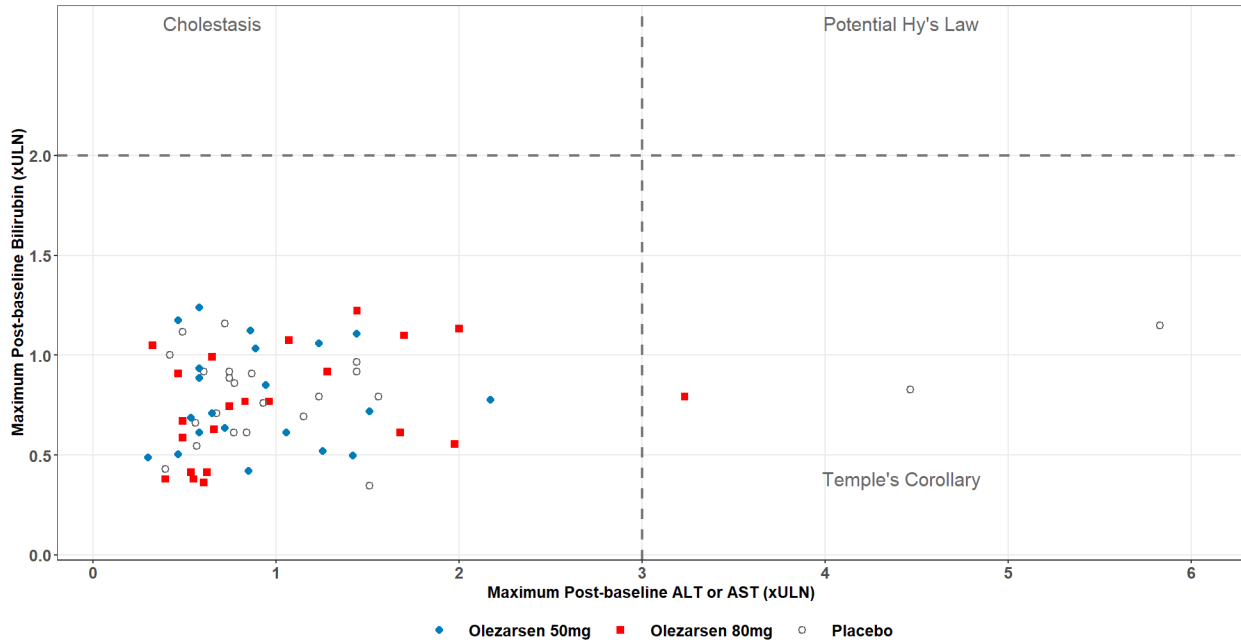
Table 72. Categorical Changes in Hepatic-Related Laboratory Values of Interest, Trials CS3 and CS8

Parameter Change	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
ALT ≥ ULN	5 (23.8)	5 (22.7)	7 (30.4)	28 (48.3)	22 (38.6)	1 (2.6)
ALT ≥3x ULN	0	0	2 (8.7)	4 (6.9)	1 (1.8)	0
ALT ≥5x ULN	0	0	1 (4.3)	2 (3.4)	0	0
ALT ≥10x ULN	0	0	0	0	0	0
AST ≥3x ULN	0	1 (4.5)	1 (4.3)	3 (5.2)	0	0
AST ≥5x ULN	0	0	0	1 (1.7)	0	0
AST ≥10x ULN	0	0	0	0	0	0
Total Bilirubin ≥2x ULN	0	0	0	0	0	0
ALT or AST ≥3x ULN and total bilirubin ≥2x ULN	0	0	0	0	0	0
GGT ≥2x ULN	6 (28.6)	2 (9.1)	6 (26.1)	18 (31.0)	14 (24.6)	7 (17.9)

Source:CS3 CSR, Table 54; CS8 CSR, Table 14.3.4.2.1.1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; OLZ, olezarsen; PBO, placebo; ULN, upper limit of normal

Figure 22. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial CS3



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

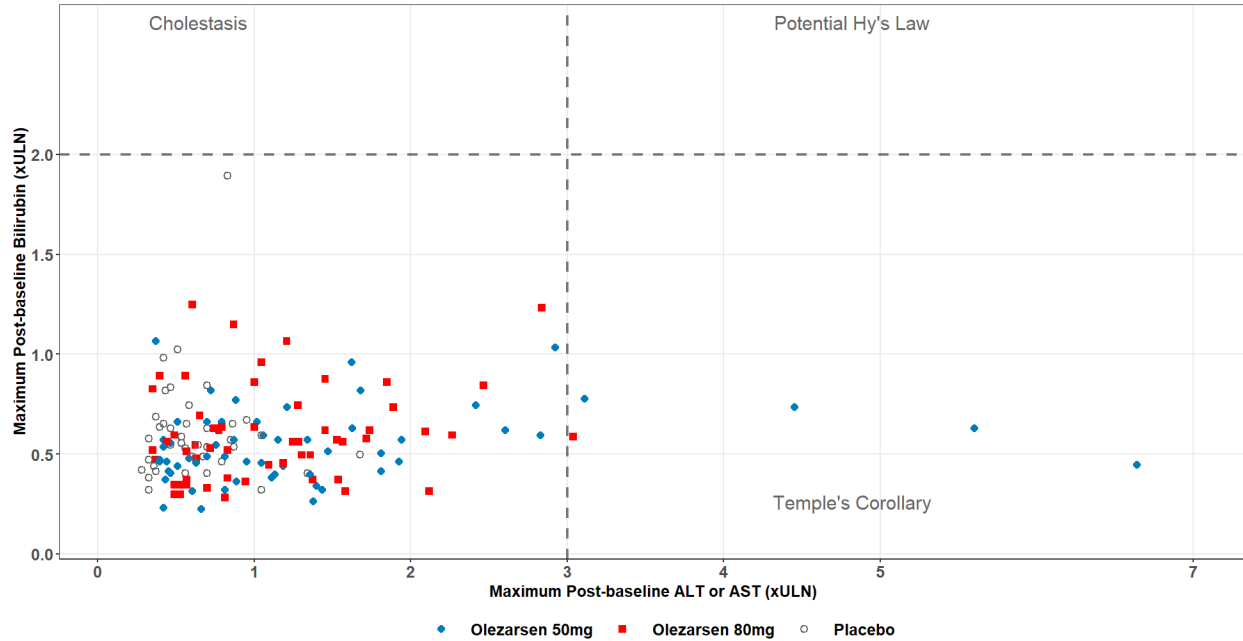
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...".

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Figure 23. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial ISIS-678354-CS8



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening..."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 73. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial ISIS-678354-CS8

Quadrant	Olezarsen 50 mg N=58 n/N _w (%)	Olezarsen 80 mg N=57 n/N _w (%)	Placebo N=39 n/N _w (%)
Potential Hy's Law (right upper)	0/58 (0)	0/57 (0)	0/39 (0)
Cholestasis (left upper)	0/58 (0)	0/57 (0)	0/39 (0)
Temple's corollary (right lower)	4/58 (6.9)	1/57 (1.8)	0/39 (0)
Total	4/58 (6.9)	1/57 (1.8)	0/39 (0)

Source: adlb.xpt; Software: R

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Note in CS8 that there were four subjects in the olezarsen 50 mg group and one subject in the olezarsen 80 mg group included in the Temple's corollary quadrant of the plot. Of these five, two continued treatment (CS8-^{(b) (6)}, CS8-^{(b) (6)}), and three discontinued treatment (CS8-

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(b) (6), CS8-(b) (6), CS8-(b) (6) due to elevations in liver enzymes. Note subject (b) (6) was lost to follow-up while study drug was interrupted and therefore was not categorized as a discontinuation due to AE.

Consultation with the Division of Hepatology and Nutrition (DHN) and the Division of Applied Regulatory Science (DARS)

Consultation with DHN and subsequently DARS was sought to further explore these hepatic transaminase increases. DARS concluded that there was (1) no suggestion of olezarsen on-target or non-specific off-target sequence effects on mRNAs in the liver that may be related to hepatic/hepatobiliary dysfunction and toxicity, (2) the olezarsen (b) (4)-linker is unlikely to be directly associated with hepatobiliary injury, (3) clinical data has shown that APOC3 inhibition by volanesorsen resulted in reduced hepatic fat fraction (HFF) in patients with diverse etiologies of severe hypertriglyceridemia (hypertriglyceridemia, familial partial lipodystrophy, and FCS), and (4) there is no evidence linking high uptake of GalNAc-conjugated-ASOs and slow/delayed release from hepatic endosomes with changes in liver function/injury or whether ASO on-target effects on the lipodome can influence endosomal function or endosomal-lysozyme systems in hepatic cells.

However, the relationship between APOC3 and liver steatosis or metabolic dysfunction-associated steatotic liver disease (MASLD) is conflicting across different studies. Information on the impact of chronic administration of olezarsen in subjects with impaired liver function is not available and has not been assessed for volanesorsen (which is an approved FCS therapy outside of the US). DARS suggests that because olezarsen and volanesorsen differ only in the (b) (4) GalNAc3-conjugate, an exploratory comparison of these ASOs in a suitable in vitro cell system (e.g., hepatic microphysiological systems, 3D-spheroids, and/or organ-on-chip approaches) may provide further information on the relationship between potential liver changes or injury and endosomal trafficking and release, and reduced APOC3-mediated changes in the transcriptome and lipodome following ASO degradation. The review team is considering this as a possible post marketing commitment.

The DHN consult, in DARRTS dated December 16, 2024, concludes that the concerning adverse events of hepatic failure or cirrhosis that occurred in FCS patients do not appear to be directly attributable to olezarsen. However, the consequence of lifetime treatment with olezarsen in FCS is unknown, particularly in those patients with underlying liver disease. DHN recommends considering a PMR or PMC assessing the potential for drug induced liver injury with Tryngolza with evaluation including baseline and periodic laboratory tests and hepatic imaging over 3 to 5 years. Description of these modest aminotransferase elevations should be included in labelling.

Conclusion

In general, the incidence of hepatic events was low and similar across treatment groups. However, olezarsen was associated with average increases in ALT, AST, GGT within the first 3 months which stabilized, and remained within reference range. There were a higher proportion of olezarsen-treated subjects in whom serious hepatic events occurred and increases in liver enzymes led to discontinuation or interruption of study drug. Liver enzymes returned towards baseline with discontinuation of olezarsen. There were no cases of Hy's Law, an indicator of

drug-induced liver injury, noted with olezarsen treatment. However, to evaluate further this potential for chronic drug-induced liver injury, we plan longer term follow-up with laboratory tests and hepatic imaging in patients with severe hypertriglyceridemia in dedicated clinical trials along with enhanced pharmacovigilance for hepatic toxicity events in patients with FCS.

7.7.4. Dysglycemia

Issue

Treatment with olezarsen did not have consistent salutary effects on glycemic control parameters in clinical trials.

Background

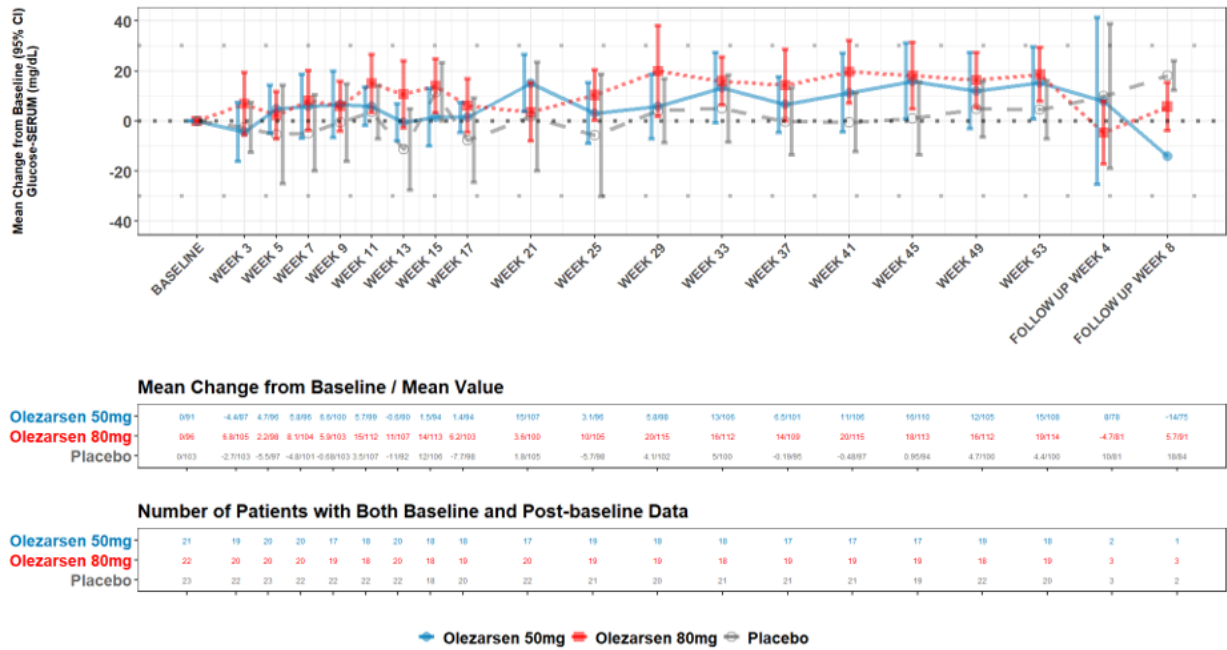
Volanesorsen showed a worsening in glycemic control in clinical studies. In a clinical trial of subjects with multifactorial chylomicronemia, in those with type 2 diabetes, the mean percent changes from baseline in HbA1c were 0.4% in the volanesorsen group and -0.2% in the placebo group; these were statistically significant ($P=0.0301$) ([Gouni-Berthold et al. 2021](#)). Per the authors of this trial, a mildly elevated baseline HbA1c in both groups and an imbalance in baseline antidiabetic therapy with 70% of subjects in the placebo group being on insulin compared to 27% of patients in the volanesorsen group, may have contributed to the observed differences. However, it is not reassuring that another ASO that also targets ApoC-III reported worsening glycemic control with drug therapy ([Gaudet et al. 2024](#)).

Assessment

In Trial CS3, average glucose and HbA1c values increased more in the olezarsen treatment groups than placebo. At baseline, mean glucose values were approximately 91 mg/dL, 96 mg/dL, and 103 mg/dL in the olezarsen 50 mg, olezarsen 80 mg, and placebo groups, respectively. At Week 53, there was an approximately 20% increase in the average glucose value in the olezarsen treatment groups (absolute mean change from baseline of 15 mg/dL in the olezarsen 50 mg group and 18 mg/dL in the olezarsen 80 mg group compared to 13% (4.5 mg/dL) increase in the placebo group (see [Figure 24](#)).

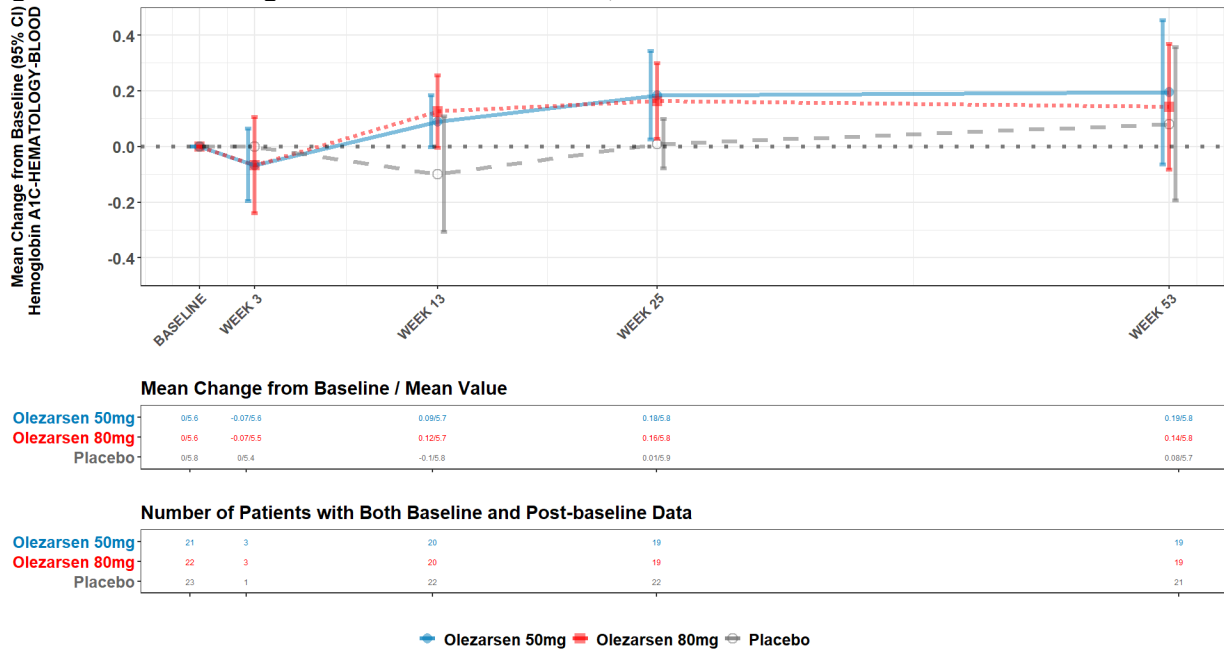
In Trial CS3, the mean HbA1c at baseline was 5.6%, 5.6%, and 5.8% in the olezarsen 50 mg, olezarsen 80 mg, and placebo treatment groups. Over time, the olezarsen treatment groups had higher average HbA1c values compared to the placebo group. At Week 53, the olezarsen 50 mg group was 0.19 percentage points higher, the olezarsen 80 mg group was 0.14 percentage points higher, and the placebo group was 0.08 percentage points higher (see [Figure 25](#)).

Figure 24. Mean Change From Baseline – Glucose (mg/dL), Trial CS3



Source: CDS reviewer graph adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Only central laboratory data are included in the analysis.
 Abbreviations: CI, confidence interval

Figure 25. Mean Change From Baseline in HbA1c, Trial CS3



Source: CDS reviewer graph adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c

In Trial CS8, glucose values at baseline were 131 mg/dL, 134 mg/dL, and 142 mg/dL in the olezarsen 50 mg, olezarsen 80 mg, and placebo treatment groups, respectively and 66% of subjects in CS8 had type 2 diabetes at baseline. At Week 53, the 50 mg olezarsen group’s average glucose value had increased approximately 9 mg/dL; olezarsen 80 mg and placebo groups’ glucose values were below baseline values by approximately 2 to 5 mg/dL.

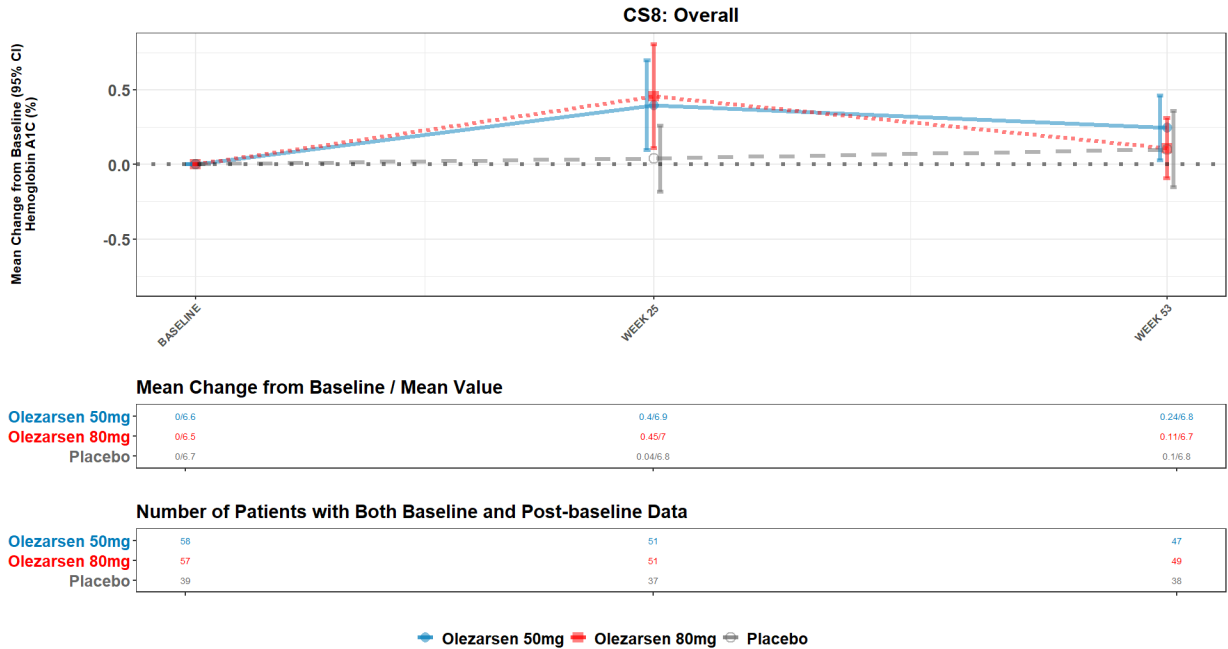
In Trial CS8, the mean HbA1c at baseline was 6.6%, 6.5%, and 6.7% in the olezarsen 50 mg, olezarsen 80 mg, and placebo treatment groups, respectively. At Week 53, the olezarsen 50 mg group was 0.24 percentage points higher, the olezarsen 80 mg group was 0.11 percentage points higher, and the placebo group was 0.10 percentage points higher (see [Figure 25](#)).

Figure 26. Mean Change From Baseline Over Time – Glucose (mg/dL), Trial CS8



Source: CDS figure adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval

Figure 27. Mean Change From Baseline Over Time – HbA1c (%), Trial CS8



Source: CDS figure adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c

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To further assess the effect of olezarsen on glucose metabolism, a hyperglycemia algorithmic FMQ was evaluated for CS3 and CS8 overall and by medical history of diabetes (see [Table 74](#)).

In CS3, overall and by diabetic status more olezarsen-treated subjects fulfilled at least one of the hyperglycemia criteria compared to placebo-treated subjects. In subjects with no history of diabetes, the proportion of subjects fulfilling ≥ 1 FMQ criterion was greater in both the olezarsen 50 mg (50%) and olezarsen 80 mg (53.3%) groups compared with the placebo group (35.3%). The most fulfilled criteria in this subgroup included “change from baseline fasting glucose ≥ 20 mg/dL with postbaseline fasting glucose >100 mg/dL” (44.4%, 53.3%, and 23.5% in the olezarsen 50 mg, olezarsen 80 mg, and placebo groups, respectively) and “HbA1c Increase $\geq 0.3\%$ with Post-Baseline HbA1c $\geq 5.7\%$ ” (27.8%, 26.7%, and 11.8%, respectively).

In CS8, a less consistent pattern was observed. In subjects without a history of diabetes, proportionally fewer subjects fulfilled ≥ 1 FMQ criterion in the olezarsen 80 mg group (31.6%) compared with the olezarsen 50 mg (57.1%) and the placebo (55.6%) group.

It is uncertain whether the differences in degree of HTG or proportion of subjects with type 2 diabetes at baseline impacts the effect of olezarsen on glucose control and contributes to the differences observed between Trials CS3 and CS8.

Table 74. Hyperglycemia-Related Algorithmic FMQ, Trials CS3 and CS8

Parameter	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
All Subjects:						
Subjects with ≥ 1 algorithmic criterion	12 (57.1)	15 (68.2)	12 (52.2)	47 (81.0)	42 (73.7)	35 (89.7)
Any Hyperglycemia FMQ Narrow term	1 (4.8)	0	3 (13.0)	8 (13.8)	7 (12.3)	5 (12.8)
Fasting glucose ≥ 126 mg/dL	6 (28.6)	6 (27.3)	5 (21.7)	41 (70.7)	40 (70.2)	33 (84.6)
≥ 2 glucose ≥ 180 mg/dL	2 (9.5)	2 (9.1)	3 (13.0)	19 (32.8)	18 (31.6)	12 (30.8)
Any new diabetic concomitant medication	0	0	2 (8.7)	8 (13.8)	11 (19.3)	8 (20.5)
Postbaseline HbA1c $\geq 6.5\%$	4 (19.0)	4 (18.2)	5 (21.7)	34 (58.6)	31 (54.4)	26 (66.7)
HbA1c increase $\geq 0.3\%$ with postbaseline HbA1c $\geq 5.7\%$	8 (38.1)	8 (36.4)	4 (17.4)	27 (46.6)	29 (50.9)	13 (33.3)
Change from BL fasting glucose ≥ 20 mg/dL with postbaseline fasting glucose >100 mg/dL	11 (52.4)	15 (68.2)	8 (34.8)	38 (65.5)	32 (56.1)	26 (66.7)
Subjects with no history of diabetes	18 (85.7)	15 (68.2)	17 (73.9)	21 (36.2)	19 (33.3)	9 (23.1)
Subjects with ≥ 1 algorithmic criterion	9 (50.0)	8 (53.3)	6 (35.3)	12 (57.1)	6 (31.6)	5 (55.6)
Any Hyperglycemia FMQ Narrow term	1 (5.6)	0	1 (5.9)	4 (19.0)	2 (10.5)	2 (22.2)
Fasting glucose ≥ 126 mg/dL	3 (16.7)	2 (13.3)	0	7 (33.3)	5 (26.3)	4 (44.4)
≥ 2 glucose ≥ 180 mg/dL	0	1 (6.7)	0	1 (4.8)	1 (5.3)	0
Any new diabetic concomitant medication	0	0	2 (11.8)	1 (4.8)	2 (10.5)	1 (11.1)
Postbaseline HbA1c $\geq 6.5\%$	1 (5.6)	1 (6.7)	1 (5.9)	3 (14.3)	2 (10.5)	0

Parameter	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
HbA1c increase $\geq 0.3\%$ with postbaseline HbA1c $\geq 5.7\%$	5 (27.8)	4 (26.7)	2 (11.8)	4 (19.0)	3 (15.8)	1 (11.1)
Change from BL fasting glucose ≥ 20 mg/dL with postbaseline fasting glucose >100 mg/dL	8 (44.4)	8 (53.3)	4 (23.5)	9 (42.9)	5 (26.3)	5 (55.6)
Subjects with history of diabetes	3 (14.3)	7 (31.8)	6 (26.1)	37 (63.8)	38 (66.7)	30 (76.9)
Subjects with ≥ 1 algorithmic criterion	3 (100)	7 (100)	6 (100)	35 (94.6)	36 (94.7)	30 (100)
Any Hyperglycemia FMQ Narrow term	0	0	2 (33.3)	4 (10.8)	5 (13.2)	3 (10.0)
Fasting glucose ≥ 126 mg/dL	3 (100)	4 (57.1)	5 (83.3)	34 (91.9)	35 (92.1)	29 (96.7)
≥ 2 glucose ≥ 180 mg/dL	2 (66.7)	1 (14.3)	3 (50.0)	18 (48.6)	17 (44.7)	12 (40.0)
Any new diabetic concomitant medication	0	0	0	7 (18.9)	9 (23.7)	7 (23.3)
Postbaseline HbA1c $\geq 6.5\%$	3 (100)	3 (42.9)	4 (66.7)	31 (83.8)	29 (76.3)	26 (86.7)
HbA1c increase $\geq 0.3\%$ with postbaseline HbA1c $\geq 5.7\%$	3 (100)	4 (57.1)	2 (33.3)	23 (62.2)	26 (68.4)	12 (40.0)
Change from BL fasting glucose ≥ 20 mg/dL with postbaseline fasting glucose >100 mg/dL	3 (100)	7 (100)	4 (66.7)	29 (78.4)	27 (71.1)	21 (70.0)

Source: CS3 CSR Table 56; CS8 CSR Table 58 Confirmed by CDS

Abbreviations: BL, baseline; CDS, clinical data scientist; CSR, clinical study report; FMQ, FDA medical query; HbA1c, hemoglobin A1c; OLZ, olezarsen; PBO, placebo

The proportion of subjects in Trials CS3 and CS8, with postbaseline glucose and HbA1c values used to define levels of impaired fasting glucose, type 2 diabetes, and hypoglycemia are shown in the tables below.

In CS3 and CS8, the olezarsen-treatment groups had a higher proportion of subjects meeting hyperglycemia cut-offs except for the category “HbA1c $\geq 6.5\%$ ”. Hypoglycemia events defined solely by glucose values were more common in Trial CS3 than in CS8. In CS3, olezarsen 50 mg treated subjects had a higher frequency of low glucose values compared to olezarsen 80 mg and placebo. No significant differences were noted compared to placebo when olezarsen treatment groups were combined.

Table 75. Summary of Postbaseline Hyperglycemia, Safety Set, Trial CS3

	Olezarsen 50 mg N=21 n/Nw (%)	Olezarsen 80 mg N=22 n/Nw (%)	Total Olezarsen N=43 n/Nw (%)	Placebo N=23 n/Nw (%)
Hyperglycemia Glucose Event				
Level 1 (fasting glucose ≥ 100 to < 126 mg/dL)	16/21 (76.2)	21/22 (95.5)	37/43 (86.0)	11/23 (47.8)
0 episode	5/21 (23.8)	1/22 (4.5)	6/43 (14.0)	12/23 (52.2)
1 episode	4/21 (19.0)	3/22 (13.6)	7/43 (16.3)	0/23 (0)
2+ episodes	12/21 (57.1)	18/22 (81.8)	30/43 (69.8)	11/23 (47.8)
Level 2 (fasting glucose ≥ 126 mg/dL or random glucose ≥ 200 mg/dL)	6/21 (28.6)	6/22 (27.3)	12/43 (27.9)	5/23 (21.7)
0 episode	15/21 (71.4)	16/22 (72.7)	31/43 (72.1)	18/23 (78.3)
1 episode	1/21 (4.8)	0/22 (0)	1/43 (2.3)	0/23 (0)
2+ episodes	5/21 (23.8)	6/22 (27.3)	11/43 (25.6)	5/23 (21.7)

Source: CDS table adsl.xpt; Software: R

Random glucose included both fasting and non-fasting glucose.

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Table 76. Summary of Postbaseline HbA1c, Safety Set, Trial CS3

	Olezarsen 50 mg N=21 n/Nw (%)	Olezarsen 80 mg N=22 n/Nw (%)	Total Olezarsen N=43 n/Nw (%)	Placebo N=23 n/Nw (%)
HbA1c				
Level 1 (fasting HbA1c $\geq 5.7\%$ to $< 6.5\%$)	9/21 (42.9)	12/22 (54.5)	21/43 (48.8)	7/23 (30.4)
0 episode	12/21 (57.1)	10/22 (45.5)	22/43 (51.2)	16/23 (69.6)
1 episode	2/21 (9.5)	4/22 (18.2)	6/43 (14.0)	1/23 (4.3)
2+ episodes	7/21 (33.3)	8/22 (36.4)	15/43 (34.9)	6/23 (26.1)
Level 2 (fasting HbA1c $\geq 6.5\%$)	4/21 (19.0)	4/22 (18.2)	8/43 (18.6)	5/23 (21.7)
0 episode	17/21 (81.0)	18/22 (81.8)	35/43 (81.4)	18/23 (78.3)
1 episode	1/21 (4.8)	1/22 (4.5)	2/43 (4.7)	1/23 (4.3)
2+ episodes	3/21 (14.3)	3/22 (13.6)	6/43 (14.0)	4/23 (17.4)

Source: CDS table adsl.xpt; Software: R

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; HbA1c, hemoglobin A1c.

Table 77. Summary of Postbaseline Hyperglycemia, Safety Set, Trial CS8

	Olezarsen 50 mg N=58 n/Nw (%)	Olezarsen 80 mg N=57 n/Nw (%)	Total Olezarsen N=115 n/Nw (%)	Placebo N=39 n/Nw (%)
Hyperglycemia Glucose Event				
Level 1 (fasting glucose $\geq$ 100 to $<$ 126 mg/dL)	43/58 (74.1)	50/57 (87.7)	93/115 (80.9)	33/39 (84.6)
0 episode	15/58 (25.9)	7/57 (12.3)	22/115 (19.1)	6/39 (15.4)
1 episode	11/58 (19.0)	8/57 (14.0)	19/115 (16.5)	5/39 (12.8)
2+ episodes	32/58 (55.2)	42/57 (73.7)	74/115 (64.3)	28/39 (71.8)
Level 2 (fasting glucose $\geq$ 126 mg/dL or random glucose $\geq$ 200 mg/dL)	41/58 (70.7)	40/57 (70.2)	81/115 (70.4)	33/39 (84.6)
0 episode	17/58 (29.3)	17/57 (29.8)	34/115 (29.6)	6/39 (15.4)
1 episode	1/58 (1.7)	5/57 (8.8)	6/115 (5.2)	1/39 (2.6)
2+ episodes	40/58 (69.0)	35/57 (61.4)	75/115 (65.2)	32/39 (82.1)

Source: CDS table adsl.xpt; Software: R

Random glucose included both fasting and non-fasting glucose.

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Table 78. Summary of Postbaseline HbA1c, Safety Set, Trial CS8

	Olezarsen 50 mg N=58 n/Nw (%)	Olezarsen 80 mg N=57 n/Nw (%)	Total Olezarsen N=115 n/Nw (%)	Placebo N=39 n/Nw (%)
HbA1c				
Level 1 (fasting HbA1c $\geq$ 5.7% to $<$ 6.5%)	24/55 (43.6)	22/53 (41.5)	46/108 (42.6)	15/39 (38.5)
0 episode	31/55 (56.4)	31/53 (58.5)	62/108 (57.4)	24/39 (61.5)
1 episode	13/55 (23.6)	11/53 (20.8)	24/108 (22.2)	6/39 (15.4)
2+ episodes	11/55 (20.0)	11/53 (20.8)	22/108 (20.4)	9/39 (23.1)
Level 2 (fasting HbA1c $\geq$ 6.5%)	34/55 (61.8)	31/53 (58.5)	65/108 (60.2)	26/39 (66.7)
0 episode	21/55 (38.2)	22/53 (41.5)	43/108 (39.8)	13/39 (33.3)
1 episode	10/55 (18.2)	7/53 (13.2)	17/108 (15.7)	8/39 (20.5)
2+ episodes	24/55 (43.6)	24/53 (45.3)	48/108 (44.4)	18/39 (46.2)

Source: CDS table adsl.xpt; Software: R

Duration is [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; HbA1c, hemoglobin A1c.

Table 79. Summary of Postbaseline Hypoglycemia, Safety Set, Trial CS3

Hypoglycemia Event	Olezarsen 50 mg N=21 n/Nw (%)	Olezarsen 80 mg N=22 n/Nw (%)	Total Olezarsen N=43 n/Nw (%)	Placebo N=23 n/Nw (%)
Level 1 (≥54 to <70 mg/dL)	9/21 (42.9)	6/22 (27.3)	15/43 (34.9)	10/23 (43.5)
0 episode	12/21 (57.1)	16/22 (72.7)	28/43 (65.1)	13/23 (56.5)
1 episode	2/21 (9.5)	2/22 (9.1)	4/43 (9.3)	4/23 (17.4)
2+ episodes	7/21 (33.3)	4/22 (18.2)	11/43 (25.6)	6/23 (26.1)
Level 2 (<54 mg/dL)	7/21 (33.3)	4/22 (18.2)	11/43 (25.6)	3/23 (13.0)
0 episode	14/21 (66.7)	18/22 (81.8)	32/43 (74.4)	20/23 (87.0)
1 episode	3/21 (14.3)	2/22 (9.1)	5/43 (11.6)	2/23 (8.7)
2+ episodes	4/21 (19.0)	2/22 (9.1)	6/43 (14.0)	1/23 (4.3)

Source: CDS table adlb.xpt; Software: R

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Table 80. Summary of Postbaseline Hypoglycemia, Safety Set, Trial CS8

Hypoglycemia Event	Placebo N=39 n/Nw (%)	Olezarsen 50 mg N=58 n/Nw (%)	Olezarsen 80 mg N=57 n/Nw (%)	Total Olezarsen N=115 n/Nw (%)	Placebo N=23 n/Nw (%)
Level 1 (≥54 to <70 mg/dL)	1/39 (2.6)	3/58 (5.2)	1/57 (1.8)	4/115 (3.5)	10/23 (43.5)
0 episode	38/39 (97.4)	55/58 (94.8)	56/57 (98.2)	111/115 (96.5)	13/23 (56.5)
1 episode	1/39 (2.6)	2/58 (3.4)	1/57 (1.8)	3/115 (2.6)	4/23 (17.4)
2+ episodes	0/39 (0)	1/58 (1.7)	0/57 (0)	1/115 (0.9)	6/23 (26.1)
Level 2 (<54 mg/dL)	0/39 (0)	1/58 (1.7)	0/57 (0)	1/115 (0.9)	3/23 (13.0)
0 episode	39/39 (100)	57/58 (98.3)	57/57 (100)	114/115 (99.1)	20/23 (87.0)
1 episode	0/39 (0)	1/58 (1.7)	0/57 (0)	1/115 (0.9)	2/23 (8.7)
2+ episodes	0/39 (0)	0/58 (0)	0/57 (0)	0/115 (0)	1/23 (4.3)

Source: CDS table adlb.xpt; Software: R

Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data

Conclusion

Small increases in average values in fasting glucose and HbA1c over time were observed with olezarsen treatment in the FCS population. In an ad-hoc analysis using an algorithmic FMQ for hyperglycemia consisting of AEs, new antidiabetic medication, and laboratory values, a higher proportion of olezarsen-treated subjects without a medical history of diabetes at baseline versus placebo-treated subjects fulfilled at least one of the FMQ criteria, suggesting a safety signal for worsening glycemic control. However, it is uncertain whether this represents a true risk with olezarsen treatment. Furthermore, glucose metabolism is monitorable and treatable, and these factors should be considered when evaluating the benefits and risks associated with olezarsen.

7.7.5. Injection Site Reactions

Issue

Treatment with olezarsen is associated with ISRs.

Background

Subcutaneously administered oligonucleotides are associated with localized reactions around the injection site, such as erythema, itching, and pain, and less commonly severe ulceration and necrosis. The reported incidence of ISRs in various oligonucleotide clinical trials ranged from 22% to 100% ([van Meer et al. 2016](#)).

Assessment

An injection site reaction was defined as a TEAE with a preferred term or verbatim term containing ‘injection site’ that persisted for at least 2 days (i.e., event resolution date not on the day of the event onset date or the day after) or was ongoing. A separate definition was also used to describe a more severe reaction defined as local cutaneous reaction at the injection site (LCRIS), which was defined as: (A) moderate or severe AEs which included the preferred terms of 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 or were ongoing; or (B) any AE at the study drug injection site, regardless of severity, that led to discontinuation of study drug, where the AE at the study drug injection site was the principal reason for discontinuation or if the AE at the injection site led to discontinuation of study drug. The severity of AEs was graded based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, which rates injection site reactions based on pain, tenderness, size of erythema/redness, and size of induration/swelling.

Using the ISR definition, in Trial CS3, a higher proportion of olezarsen-treated subjects reported an ISR compared to placebo-treated subjects (see [Table 81](#)). None of the ISRs were serious and no subjects reduced study drug, withdrew from the trial, or required treatment of the ISR. The median number of injections received before the first ISR was 2 in the olezarsen 50 mg group, 3 in the olezarsen 80 mg group, and 3 in the placebo group. The median duration of the ISR was 42 days in the 50 mg olezarsen group, 6 days in the 80 mg olezarsen group, and 133 days in the placebo group. Two of the eight subjects’ injection site reactions (one placebo ‘IS discoloration’, and one olezarsen 50 mg ‘IS erythema’) had not recovered or resolved at the data cut-off.

There were no events in Trial CS3 that met the definition of an LCRIS.

In the OLE study, CS13, five subjects previously treated with placebo who started olezarsen reported 40 ISR events. One subject in the olezarsen-naïve treatment group reported 33 of these events. For this individual (# ██████████^{(b) (6)}), the events were ‘injection site discoloration’ that was reported as not resolved, ‘injection site erythema’, ‘injection site swelling’, and ‘injection site hematoma’. This study subject also experienced a TEAE of hepatic enzyme increased that led to permanent discontinuation of study drug. The study site noted that the ISR discoloration event had resolved 1 month after the last follow-up post-treatment visit.

Individuals who had been treated with olezarsen in the index trial and continued with olezarsen in the open-label extension, reported fewer events – five olezarsen-treated subjects in CS3 reported seven events in CS13. No events were reported as serious, none met the LCRIS definition, and no subjects discontinued treatment due an ISR.

Table 81. Injection Site Reactions, Safety Population, Trial CS3

Injection Site Reactions	OLZ	OLZ	PBO	OLZ	OLZ	PBO
	50 mg N=21 n (%)	80 mg N=22 n (%)	N=23 n (%)	50 mg Events	80 mg Events	Events
Subjects reporting ≥ ISR	3 (14.3)	3 (13.6)	2 (8.7)	5	4	2
Injection site erythema	1 (4.8)	2 (9.1)	1 (4.3)	3	2	1
Injection site bruising	0	1 (4.5)	0	0	1	0
Injection site inflammation	0	1 (4.5)	0	0	1	0
Injection site discoloration	1 (4.8)	0	1 (4.3)	1	0	1
Injection site pain	1 (4.8)	0	0	1	0	0

Source: CS3 CSR, Table 14.3.2.5 (confirmed by clinical reviewer – adae.xpt dataset)
Abbreviations: ISR, injection site reaction; OLZ, olezarsen; PBO, placebo

In Trial CS8, no placebo-treated subjects had an ISR compared with 17% in the olezarsen 50 mg group and 5% in the olezarsen 80 mg group (see [Table 82](#)). Within the group with ISRs, there were four subjects in the olezarsen 50 mg group, with events that met the definition for a LCRIS due to discontinuing treatment due an injection site AE. Another subject in the olezarsen 80 mg group, reduced their study dose due to an ISR.

The median number of injections received before the first ISR was 3.5 and 1 in the olezarsen 50 mg and 80 mg treatment groups, respectively. The median duration of an ISR was 24 days and 174 days in the olezarsen 50 mg and 80 mg treatment groups, respectively. For an LCRIS, the median duration was 80 days.

At the time of data cutoff, 2 of the 13 subjects that reported ISRs (injection site bruising; injection site erythema) had not resolved. All subjects that discontinued treatment due to an AE at the injection site reported the event had recovered/resolved.

Table 82. Injection Site Reactions, Safety Population, Trial CS8

Injection Site Reactions	OLZ	OLZ	PBO	OLZ	OLZ	PBO
	50 mg	80 mg		50 mg	80 mg	
	N=58	N=57	N=39	50 mg	80 mg	PBO
	n (%)	n (%)	n (%)	Events	Events	Events
Subjects reporting ≥ ISR	10 (17.2)	3 (5.3)	0	19	6	0
Injection site erythema*	7 (12.1)	2 (3.5)	0	10	4	0
Injection site discoloration	2 (3.4)	0	0	2	0	0
Injection site hemorrhage*	2 (3.4)	0	0	2	0	0
Injection site bruising	0	1 (1.8)	0	0	2	0
Injection site pain	1 (1.7)	0	0	1	0	0
Injection site pruritus*	1 (1.7)	0	0	2	0	0
Injection site reaction	1 (1.7)	0	0	1	0	0
Injection site urticaria*	1 (1.7)	0	0	1	0	0

Source: CS8 CSR Table 14.3.1.2.5 (confirmed by clinical reviewer – adae.xpt)

*This adverse event resulted in study drug discontinuation for at least 1 subject thus qualifying as a LCRIS

Abbreviations: ISR, injection site reaction; OLZ, olezarsen; PBO, placebo

In the open-label study, CS7, four (16.7%) subjects reported 56 ISR events, 32 of these were ‘injection site erythema’ and 14 were ‘injection site discoloration’. Of these four subjects, one reported injection sites of moderate severity, thus qualifying as an LCRIS. This subject (# (b) (6)) reported ISRs starting with the first dose and subsequent doses. The day of the 8th dose of study drug, the subject reported injection site erythema, swelling, and pain of moderate severity. No action was taken with regard to study drug, and 4 days later the events were recovered/resolved. The subject continued to report ISRs, for example on Study Days 226, 254, 282, and 308 (last day before data cutoff) the subject reported ‘injection site discoloration’ while continuing olezarsen treatment. In CS7, the mean duration of injection site discoloration was 261 days.

Conclusion

Injection site reactions occur with olezarsen treatment and are characterized primarily by erythema and discoloration. The median number of injections before the first ISR ranged from 1 to 3. In the FCS controlled trial, CS3, the number of injection reaction site events was small (total events in olezarsen-treated [50 and 80 mg combined] group was 9 in 6 [14%] subjects). This may be an underestimation of the number of events given that in the open-label studies of FCS, 10 (19%) subjects in CS13 reported a total of 47 events, and in CS7, 4 (17%) subjects reported 56 events. None of the injection site reactions were serious, and no subjects in FCS trials reduced study drug, withdrew from the trial, or required treatment of the ISR. The majority of injection site reactions resolved, however the duration of ISRs of discoloration and erythema was variable (several days to months before resolution). The incidence of injection site reactions will be described in section 6.1 of the PI.

7.7.6. Increase in LDL-C

Issue

In the FCS trial, CS3, treatment with olezarsen was associated with increases in LDL-C and total ApoB. These directional shifts are conventionally considered adverse in assessments of

cardiovascular risk. The clinical impact of olezarsen’s effect on lipids in this population is uncertain.

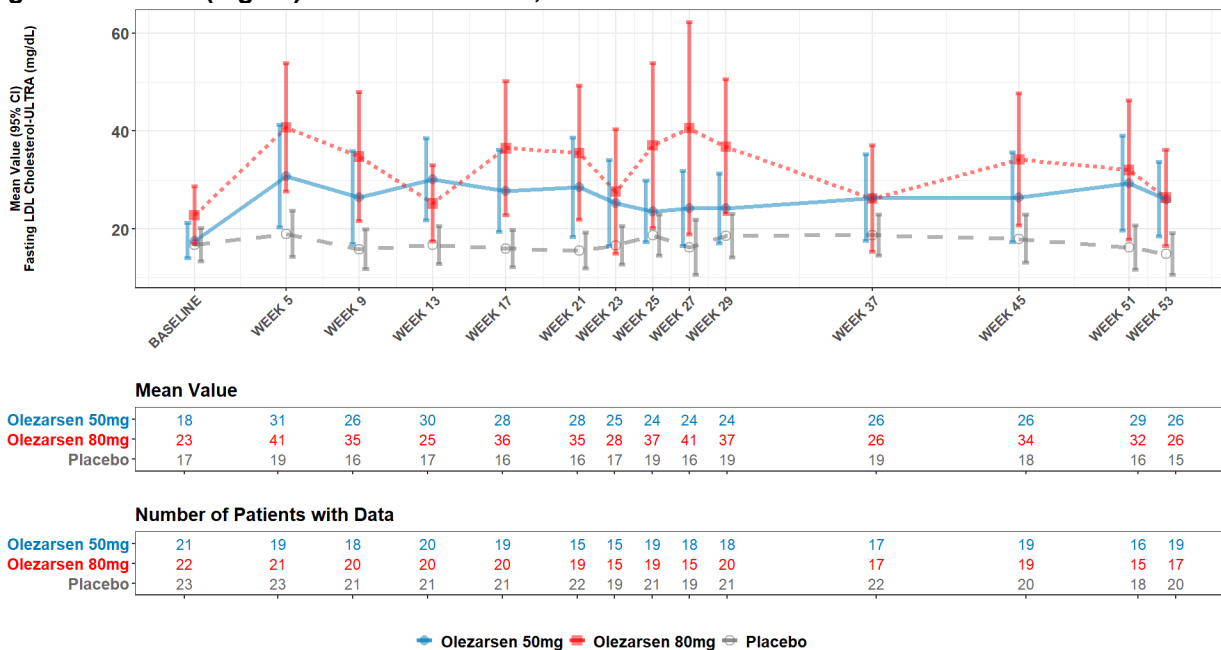
Background

Several drug classes induce lipid abnormalities including anti-hypertensives (thiazide diuretics [increase cholesterol and TG], certain beta blockers [increase TG, decrease HDL-C]), immunosuppressants (cyclosporine and tacrolimus), protease inhibitors (increase LDL-C), antipsychotic drugs (increase TG), SGLT2 inhibitors (increase LDL-C), and fish oil derived prescription products (increase LDL-C). Volanesorsen in clinical trials increases LDL-C. This may be due to increased lipolysis of TG, although the mechanism has not been conclusively determined.

Assessment

In CS3, treatment with olezarsen resulted in elevations in LDL-C. At Month 12, the least square mean percent change in LDL-C from baseline increased in the olezarsen 50 mg and olezarsen 80 mg groups by 53% and 47%, respectively versus -0.1% in the placebo group. However, because individuals with FCS have very low LDL-C at baseline, the mean LDL-C values at Month 12 were 27 mg/dL, 29 mg/dL and 16 mg/dL in the olezarsen 50 mg, olezarsen 80 mg, and placebo groups, respectively (see [Figure 28](#)).

Figure 28. LDL-C (mg/dL) Values Over Time, Trial CS3



Source: CDS figure adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol

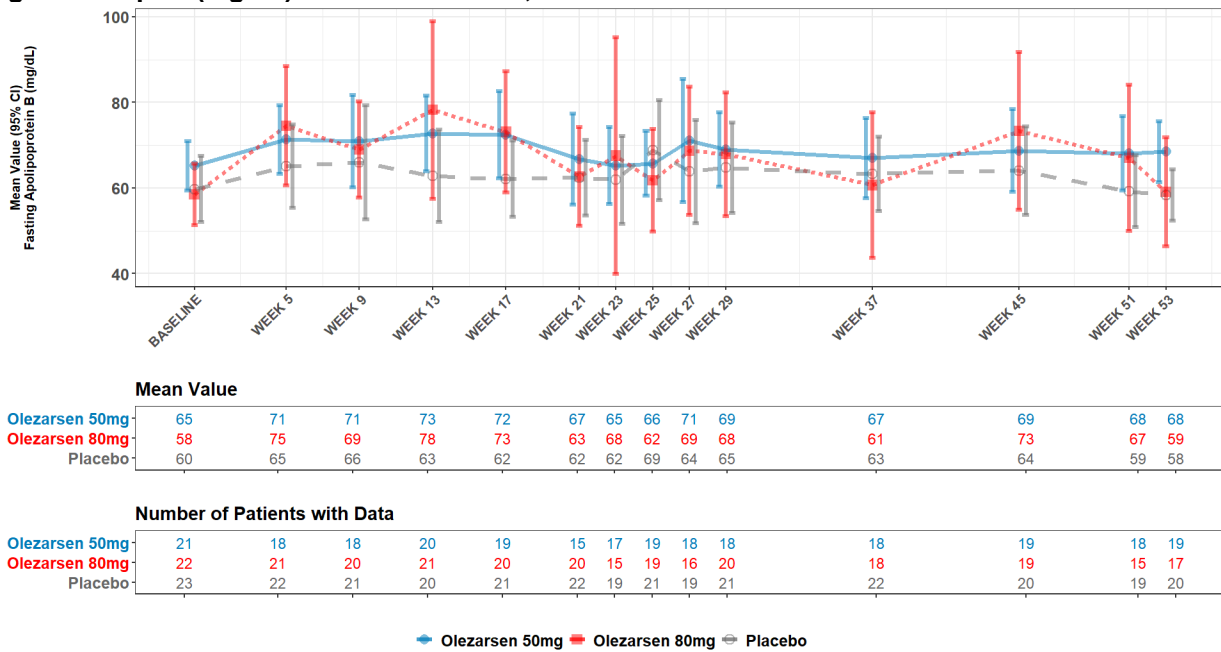
A higher proportion of subjects in Trial CS3 treated with olezarsen compared to subjects treated with placebo shifted to a worse maximum LDL-C category from their baseline LDL-C category⁵.

⁵ LDL-C categories <70; 70 to <100; 100 to <130; 130 to <160; 160 to >190; ≥190 mg/dL

All subjects at baseline had an LDL-C <70 mg/dL. No placebo-treated subjects had a postbaseline LDL-C over 70 mg/dL compared to four (19%) olezarsen 50 mg treated subjects and six (27%) olezarsen 80 mg treated subjects. No subject in the olezarsen 50 mg group, but three subjects in the olezarsen 80 mg group experienced an adverse shift of ≥ 2 severity categories in LDL-C; two subjects shifted from below 70 mg/dL to the LDL-C category of 100 to <130 mg/dL and one subject shifted from below 70 mg/dL to the LDL-C category of 130 to <160 mg/dL. These subjects were not on LDL-C lowering medications (e.g., statins) before the trial and they were not started on LDL-C lowering medications for these elevations. LDL-C values in these subjects trended down over time but remained above baseline values.

ApoB also increased with olezarsen treatment. At Month 12, a 0.6% least squares (LS) mean change from baseline was noted in the placebo group, and a 1.6% and 7.8% increase from baseline in the olezarsen 50 mg and olezarsen 80 mg groups, respectively. A higher percentage of subjects in the olezarsen treatment groups exceeded the ApoB threshold of 130 mg/dL at any time postbaseline (10% olezarsen 50 mg; 38% olezarsen 80 mg; 4% placebo).

Figure 29. ApoB (mg/dL) Values Over Time, Trial CS3

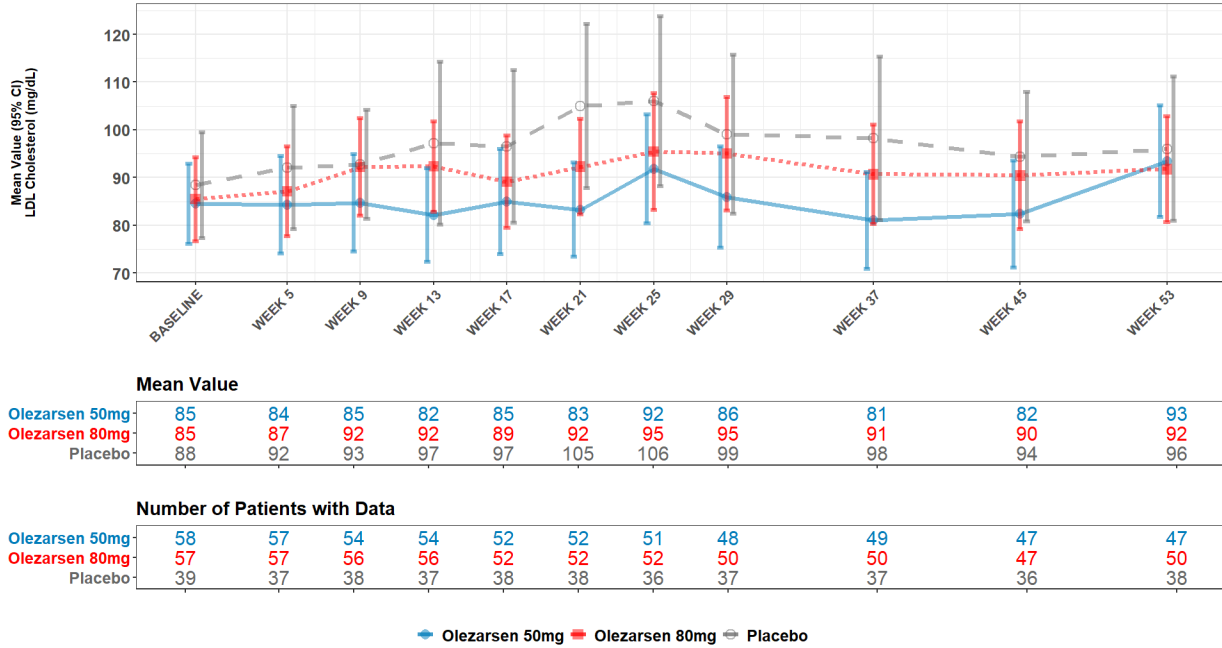


Source: CDS figure adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: apo, apolipoprotein; CI, confidence interval

In Trial CS8, all groups demonstrated increases in LDL-C over time, however, compared to placebo, mean and percent changes in LDL-C from baseline were numerically smaller in the olezarsen-treated groups. At baseline, LDL-C values were 85, 86, and 88 mg/dL in the olezarsen 50 mg, olezarsen 80 mg, and placebo groups, respectively. At Month 12 (average of Weeks 51 and 53), LS mean percent change in LDL-C from baseline was 15% in the olezarsen 50 mg group, 10% in the olezarsen 80 mg group, and 18% in the placebo group. A greater proportion of patients in the placebo group with baseline LDL-C levels < ULN (<130 mg/dL) experienced a shift to a maximum postbaseline level $\geq$ ULN (14/35 [40.0%] patients) compared with the olezarsen 80 mg group (16/52 [30.8%] patients) and the olezarsen 50 mg (16/52 [30.8%] patients)

patients) group. Two subjects (one in each olezarsen treatment group started treatment with a statin during the trial).

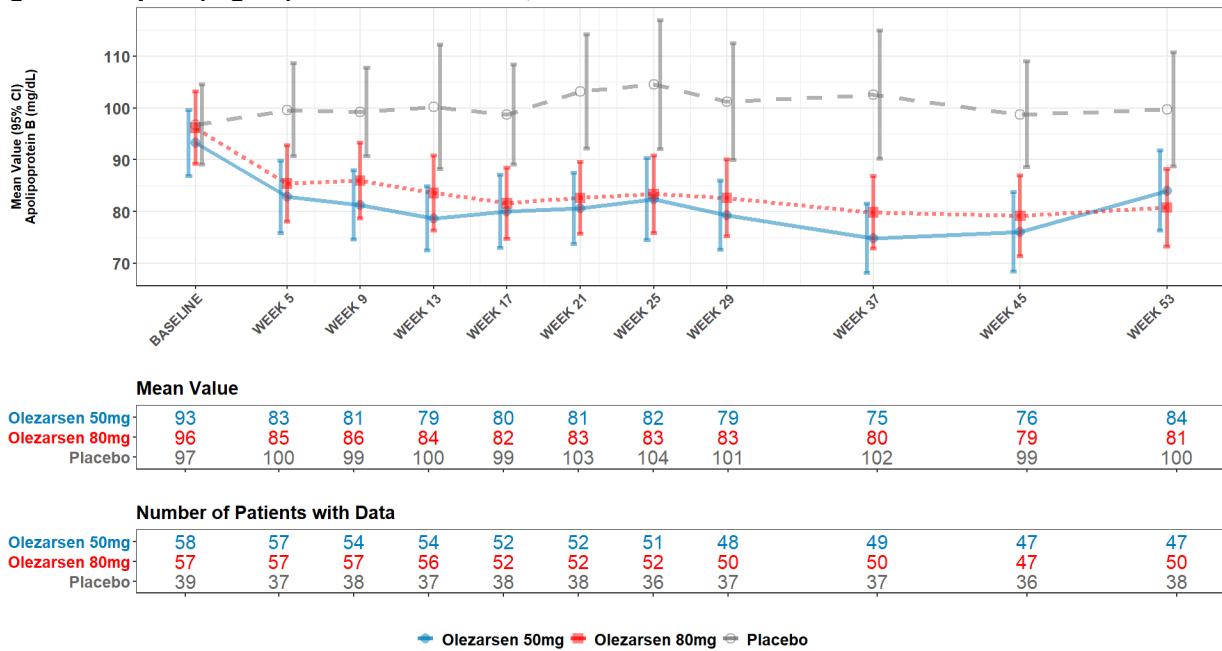
Figure 30. LDL-C (mg/dL) Values Over Time, Trial CS8



Source: CDS figure adefx.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol

ApoB in CS8 decreased in general with olezarsen treatment. ApoB at Month 12 showed a ~3% LS mean change increase from baseline in the placebo group, and a 11% and 17% LS mean decrease from baseline in the olezarsen 50 mg and olezarsen 80 mg groups, respectively.

Figure 31. ApoB (mg/dL) Values Over Time, Trial CS8



Source: CDS figure adefx.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Abbreviations: apo, apolipoprotein; CI, confidence interval

In Trial CS7, 22 out of 24 subjects at baseline had LDL-C below 70 mg/dL, and 4 subjects shifted to a higher LDL-C category. Three (12.5%) subjects had increases ≥ 2 categories from baseline, both of which were transient. One (4.2%) subject had a shift from <70 mg/dL at baseline to 130 to <160 mg/dL postbaseline, 1 (4.2%) subject had a shift from <70 mg/dL to 160 to <190 mg/dL postbaseline, and 1 (4.2%) subject had a shift from 100 mg to <130 /dL to 160 to <190 mg/dL postbaseline – this last subject was started on rosuvastatin 10 mg and ezetimibe 10 mg during the study.

Conclusion

LS mean increases in LDL-C and ApoB of approximately 50% and 8% from baseline, respectively, were noted in the FCS population treated with olezarsen 80 mg compared to a $<1\%$ LS mean increase in those treated with placebo. In contrast, in Trial CS8 of subjects with moderate to high levels of TG, LDL-C increases were smaller and similar across treatment groups, notably ApoB had a moderate decrease. It is uncertain, if the difference in LDL-C changes between the two trials is related to the degree of TG elevation at baseline and resulting lipid metabolism following ApoC-III inhibition. The clinical impact of these changes in the FCS population is uncertain, in part because despite increases in LDL-C, the value remains low (i.e., <70 mg/dL) for most study subjects. LDL-C is monitorable and could be mitigated with lipid-modifying therapy.

7.7.7. Imbalance in Cardiovascular Events

Issue

In the phase 2 trial, CS2, a higher number of serious cardiac disorders were observed in the olezarsen treatment group compared to the placebo group in a non-FCS population with moderately elevated TG at high risk for CVD. The effect of olezarsen on cardiovascular risk is unknown.

Background

Genetic studies of loss of function variants in the *apoC-III* gene showed a decrease in TG levels and risk of atherosclerotic disease ([Tg et al. 2014](#); [Wulff et al. 2018](#)). This observation has made ApoC-III a pharmaceutical target for reduction of cardiovascular risk. However, it is unknown whether a pharmacologic reduction in ApoC-III will translate into a clinical benefit of CV risk reduction. Recent trials that have focused on lipid endpoints other than LDL-C illustrate the limitations of lipid parameters as surrogates. A notable recent example is the PROMINENT trial, a cardiovascular outcome trial of pemafibrate, in statin-treated subjects with type 2 diabetes and moderate HTG which failed to show a cardiovascular benefit despite a placebo-adjusted 26% reduction in TG, and placebo-subtracted decreases in ApoC-III of 28%, but not ApoB (4.8%) ([Das Pradhan et al. 2022](#)).

Assessment

In CS3, CS8, CS7, and CS13 all AEs and SAEs that were consistent with a MACE were adjudicated by a blinded, independent committee. Trial CS2, an early phase study of olezarsen did not have a MACE adjudication committee.

In Trial CS2, a dose-finding study of olezarsen (10 mg to 50 mg) in subjects with mixed dyslipidemia there was a higher incidence of cardiac disorders in the pooled olezarsen group (13.3%) compared to the placebo group (4.2%), including a fatal cardiac arrest in the 15 mg every 2 weeks group. Serious cardiovascular events also occurred in a higher proportion of olezarsen-treated subjects (n=6 [6.7%]) compared to placebo-treated subjects (n=1 [4.2%]). A listing of the cardiovascular SAEs is listed below. Review of the narratives for these subjects was notable for a significant medical history of CVD which confounds a causality assessment.

Table 83. Listing of Serious Cardiovascular Events, Trial CS2

Subject ID Age/Race/Sex	Treatment Group	SAE (Preferred Term)	Study Day	Action Taken	Outcome	Medical History	Comment
(b) (6) 69Y/WM	Placebo	Cerebral ischemia	29	None	Recovered	Afib, pacemaker, T2DM, CABG, PCI, heart valve surgery	Visual defect noted. CT scan confirmed cerebral ischemia. Discontinued drug due to starting anticoagulant therapy
(b) (6) 80Y/WM	OLZ 10 mg Q4W	Acute coronary syndrome	121	None	Recovered	T2DM, PCI, HF, HTN	Chest pain, SOB, urgent catheterization and stent
(b) (6) 69Y/WM	15 mg Q2W	Angina unstable	43	None	Recovered	Former smoker, HTN, AMI, CABG, PCI	Chest pain, coronary catheter and stent placement
(b) (6) 63Y/WM	15 mg Q2W	Cardiac arrest	90	Drug withdrawn	Fatal	T2DM, PCI, CABG, HF, HTN	See narratives Section 7.6.3.2. No autopsy
(b) (6) 58Y/WM	50 mg Q4W	Acute myocardial infarction	168	None	Recovered	T2DM, CABG, PCI, aortic stenosis, non ST-segment elevation MI	Presented to ED with chest pain
(b) (6) 53Y/WF	50 mg Q4W	Cardiomyopathy	248	None	Recovered	T2DM, HTN, HF	Worsening nonischemic cardiomyopathy EF<25% (EF of 45% in (b) (6))
(b) (6) 69Y/WM	50 mg Q4W	Supraventricular tachycardia	436 (98 days post-last dose)	None	Recovered	Current smoker, HTN, ST-segment elevation MI, PCI	SVT occurred concurrently with pneumonia
		Pneumonia		None	Recovered		

Source: CSR CS2 Table 2, confirmed adae.xpt, patient narratives

Abbreviations: afib, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CT, computed tomography; ED, emergency department; EF, ejection fraction; F, female; HF, heart failure; HTN, hypertension; M, male; MI, myocardial infarction; PCI, percutaneous coronary intervention; Q2W, every two weeks; Q4W, every four weeks; SOB, shortness of breath; SVT, supraventricular tachycardia; T2DM, type 2 diabetes mellitus; W, white

In CS3, the number and percentage of subjects reporting an event in the SOC of cardiac disorders was relatively low (<10%); two (9.5%) subjects in the olezarsen 50 mg group, one (4.5%) subject in the olezarsen 80 mg group, and no subjects (0%) in the placebo group reported an event. No event in the cardiac SOC was serious or led to treatment discontinuation. Note that the AE of ‘sudden death’ that occurred in the olezarsen 50 mg treatment group is not reflected in the cardiac SOC terms but was adjudicated as a MACE.

In CS8, three (5.2%) subjects in the olezarsen 50 mg group, two (3.5%) in the olezarsen 80 mg group and three (7.7%) in the placebo group reported an event in the cardiac disorders SOC. No subjects in the placebo group had a serious cardiac event; whereas all five of the olezarsen-treated subjects had a serious cardiac event; only one subject discontinued treatment due this event (preferred term ‘atrial fibrillation’ – this event was not adjudicated as a MACE). Of the five subjects with a SAE in the cardiac disorder SOC, two olezarsen 50 mg treated subjects’ events were adjudicated as MACE. Note that the AE of ‘sudden death’ that occurred in the olezarsen 50 mg group, and the lacunar infarction that occurred in the olezarsen 80 mg group are not reflected in the cardiac SOC terms, both of these events were adjudicated as MACE ([Table 85](#)).

Table 84. Serious Adverse Events in the Cardiac SOC, Trial CS8

Adverse Event	OLZ	OLZ	PBO
	50 mg N=58 n (%)	80 mg N=57 n (%)	N=39 n (%)
Cardiac disorders (SOC)	3 (5.2)	2 (3.5)	0
Acute myocardial infarction	1 (1.7)*	0	0
Angina pectoris	0	1 (1.8)	0
Atrial fibrillation	1 (1.7)	0	0
Coronary artery disease	1 (1.7)*	0	0
Left ventricular failure	1 (1.7)*	0	0
Tachycardia	0	1(1.8)	0

Source: CDS STF report

*Events adjudicated as MACE

Abbreviations: OLZ, olezarsen; PBO, placebo; SOC, system organ class

A notable SAE that led to discontinuation that was not adjudicated as MACE, is briefly described here.

Subject CS8- (b) (6) – 52-year-old man with HTG with a history of hypertension, obesity, type 2 diabetes, diabetic neuropathy, and exertional dyspnea, randomized to olezarsen 50 mg. Concomitant medications included atorvastatin, allopurinol, glipizide, lisinopril, metformin, celecoxib, risperidone, and sertraline. Seven days after receiving olezarsen 50 mg, subject experienced SAE of atrial fibrillation on Study Day 147. Subject was at the study site for a repeat urine chemistry test, which was not performed because he became diaphoretic, short of breath, and complaining of chest pain. HR was noted to be 148 bpm. Emergency Medical Services took the subject to the Emergency Department. While enroute, the subject experienced atrial fibrillation (HR of 250 bpm). He was admitted with a ventricular heart rate of 130 bpm, QTc of 544 msec, and atrial flutter of 272. Chest x-ray revealed cardiomegaly. CT angiogram ruled out pulmonary embolus but revealed cardiomegaly. A 2D doppler transesophageal echocardiogram showed ejection fraction of 25-30%, a severely depressed overall left ventricular systolic function, mildly enlarged left ventricle size, Grade 1 diastolic dysfunction, and moderate right

ventricle systolic function, tricuspid regurgitation, no evidence of pericardial effusion, and a dilated inferior vena cava with poor inspiratory collapse was noted, consistent with elevated right atrial pressure. Abnormal laboratory test results included carbon dioxide of 20 mmol/L (RR: 22-29 mmol/L) and a high troponin I level of 0.034 ng/mL (RR: 0.0-0.028). On [REDACTED] (b) (6) (Study Day 148), the patient underwent a cardiac catheterization. The procedure revealed the following: angiographically normal epicardial coronary arteries, severe left ventricular systolic dysfunction, moderate to severe pulmonary hypertension with a PA pressure of 61/46 and RV pressure of 58/19. Pulmonary capillary wedge pressure was noted at 33, left ventricular end diastolic pressure varied between 21-47 depending upon the respiratory variation. Additionally, a significantly elevated RA pressure of 33/47 with a mean of 29 mmHg was noted. On the same day, non-serious TEAEs of left ventricular dysfunction and right ventricular failure were reported. On [REDACTED] (b) (6) (Study Day 150), a successful DC cardioversion to normal sinus rhythm was performed. On [REDACTED] (b) (6) (Study Day 152), the event of atrial fibrillation was considered recovered/resolved and was patient was discharged from the hospital. No action was taken with the Study Drug as a result of the event.

The MACE Adjudication Committee adjudicated the event as not MACE.

On [REDACTED] (b) (6) (Study Day 164), the patient experienced a second SAE of atrial fibrillation. He presented to the emergency department with worsening shortness of breath and palpitations which were ongoing on for last couple of days. He denied having any fever, chills, cough, or sputum. His vitals were as follows: HR of 122 bpm, RR of 18 bpm, BP of 130/94 mmHg, body temperature of 36.6 °C, and oxygen saturation (SpO₂) of 95%. His height and weight were 1.88 m and 190.5 kg, respectively, with a body mass index of 53.92 kg/m². His ECG results revealed the following: atrial flutter with HR of 130, QRS duration of 104 ms, QT of 324 ms, and QTc of 477 ms. His chest X-ray was consistent with the one conducted on Study Day 147. Abnormal laboratory test results were yielded for the following: white blood cells of $11.04 \times 10^3/\mu\text{L}$, hemoglobin of 11.5 g/dL, red blood cells of $4.16 \times 10^6/\mu\text{L}$ (RR: 4.5-5.9), hematocrit of 36.5% (RR: 41-53%), BNP of 124.1 pg/mL (RR: 0-87), prothrombin time of 16.4 s (RR: 10.3-13.3) and PTT of 38.6 s (RR: 25.1-36.5). The patient's troponin level was normal at 0.010 ng/mL (RR: 0-0.028). During hospitalization, the patient was treated with metoprolol, lisinopril, diltiazem, dofetilide, albuterol-ipratropium, carvedilol, apixaban and paracetamol for the event.

On [REDACTED] (b) (6) (Study Day 168) patient recovered from the second event of atrial fibrillation and was subsequently discharged from the hospital. As a result of the event, the Study Drug was permanently discontinued.

The MACE Adjudication Committee adjudicated the event as not MACE.

There was one SAE in CS13 of hypertensive heart disease in an olezarsen 80 mg treated subject that was not adjudicated MACE. There were no SAEs of cardiac SOC in CS7.

Adjudicated MACE

In Trial CS3, there was a sudden death in an olezarsen 50 mg treated subject that was adjudicated as a MACE. There were no MACE in the 80 mg olezarsen or placebo-treated groups.

Using the original NDA cutoff date, in Trial CS8, three (5.2%) subjects in the olezarsen 50 mg group and one (1.8%) subject in the olezarsen 80 mg group experienced a total of 7 adjudicated

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MACE; no subjects in the placebo group reported a MACE ([Table 85](#)). Note for the one death in CS8, the MACE Adjudication Committee was unable to determine whether the event was MI or heart failure. In the 90-day safety update, an additional subject in the olezarsen 80 mg group had an adjudicated MACE in the post-treatment follow-up period of hospitalization for unstable angina (preferred term triggering adjudication ‘atrial fibrillation’).

There was no adjudicated MACE in CS7 or CS13 reported with the original cutoff date. However, in the 90-day safety update, there was an adjudicated stroke event in a subject treated with 80 mg olezarsen in the open-label trial, CS13.

Table 85. Adjudicated MACE, Trials CS3, CS8, and CS13

Trial	Subject ID	Treatment Group	SAE (Preferred Term)	Adjudication Result	Study Action Day Taken	Outcome
CS3	(b) (6)	OLZ 50 mg	Sudden death	Death	42 Drug Withdrawn	Fatal
CS8	(b) (6)	OLZ 50 mg	Death	Death	206	Fatal
		OLZ 50 mg	Acute myocardial infarction	Hospitalized for Unstable Angina PCI	154 Dose not changed	Recovered/ Resolved
		OLZ 50 mg	Left ventricular failure	Heart Failure	100 Dose not changed	Recovered/ Resolved
			Coronary artery disease	PCI Hospitalized for Unstable Angina	391 Dose not changed	Recovered/ Resolved
		OLZ 80 mg	Lacunar infarction	Stroke	257 Dose not changed	Recovered/ Resolved
		OLZ 50 mg	Atrial fibrillation	Hospitalized for Unstable Angina	440 Dose not changed (Last dose of drug received on Study Day 339)	Recovered/ Resolved
CS13	(b) (6)	OLZ 80	Cerebrovascular accident	Stroke	254 Dose not changed	Ongoing

Source: .CSRs CS3, CS8, CS13, 90 day safety update, response to FDA IR submitted 6 September 2024 (SDN27), adadj.xpt
Abbreviations: MACE, major adverse cardiovascular events; OLZ, olezarsen; PCI, percutaneous coronary intervention

Conclusion

In the olezarsen clinical development program there was a higher number of deaths, serious cardiac events, and adjudicated MACE with olezarsen treatment compared to placebo treatment. There were no deaths or MACE in the placebo treatment groups. Most of the serious cardiac events and MACE occurred in a non-FCS population with underlying cardiovascular comorbidities. It is this reviewer's opinion that the number of MACE and duration of exposure is too small to provide a definitive causality assessment for olezarsen. Ongoing larger studies in subjects without FCS with either sHTG or moderate HTG at risk for or with established ASCVD may provide further information to inform this safety review issue. At this time there is no clear signal of cardiovascular harm in the FCS population, and the small imbalance in serious cardiac events associated with olezarsen treatment in the non-FCS population is likely the play of chance.

7.7.8. Immunogenicity

Issue

Treatment with olezarsen results in the development of ADA, therefore an immunogenicity assessment to evaluate the potential impacts of olezarsen ADA on safety is a review issue.

Assessment

The immunogenicity of olezarsen was evaluated in all clinical trials. In CS3 and CS8, ADA were collected at baseline (Day 1 pre-dose), Weeks 2, 5, 9 (CS3 only), 13, 25, 37, 53, and during the follow-up period (Weeks 4, 8, 13). Subjects who experienced persistent or increasing constitutional symptoms were to have additional testing for ADA status.

Subjects were given 'positive' ADA status if they had at least one confirmed positive sample at any time during the treatment or post-treatment evaluation periods. Subjects were given 'negative' ADA status if all evaluated immunogenicity sample results during the treatment and post-treatment evaluation periods were negative, and they had at least one evaluable immunogenicity sample postdose. Otherwise, study subjects were given 'unknown' ADA status.

In CS3, 24 (36.4%) of the 66 subjects at baseline were positive for anti-olezarsen ADA across treatment groups. The placebo group had the highest percentage of subjects positive for ADA at baseline (43.5%) compared to the olezarsen 50 mg (38.1%) and olezarsen 80 mg (27.3%) groups. Of note, 26 out of the 66 subjects had been previously treated with volanesorsen. Of those previously treated with volanesorsen, 14 (53.8%) were positive for ADA at baseline in Trial CS3.

No placebo-treated subjects developed treatment-emergent ADA compared to 38.1% of subjects in the olezarsen 50 mg group and 45.5% of subjects in the olezarsen 80 mg group. All subjects with induced treatment-emergent ADA had a persistent response. Of the 42 subjects who were ADA negative at baseline, 29 (69%) remained negative throughout the study. The median time to onset of treatment-emergent ADAs were similar in treatment groups that received olezarsen (30.0 days and 29.5 days in the olezarsen 80 mg group and olezarsen 50 mg group, respectively). The median time to peak titer was greater in the olezarsen 80 mg group than in the olezarsen

50 mg group (218.5 days vs. 29.5 days, respectively). The median (range) peak titer was 200 (50, 25,600) in the olezarsen 80 mg group, and 75 (50, 25,600) in the olezarsen 50 mg group.

In the OLE study, CS13, treatment-emergent ADAs were detected in 30%, 52.9%, and 88.2% of subjects for the CS3-placebo, CS3-olezarsen 50 mg, and CS3-olezarsen 80 mg groups, respectively, suggesting the incidence of treatment-emergent ADA may increase with treatment duration. At least one ISR was experienced by 26.7% of patients with treatment-emergent ADAs in comparison with 6.3% and 12.5% of patients with negative ADA status and treatment-unaffected ADA, respectively. Hypersensitivity events were only experienced by patients with treatment-emergent ADAs (23.3%). Two subjects (CS3 (b) (6) and CS3 (b) (6)) experienced serious hypersensitivity events in CS13 and also had high ADA titers. See Section 7.7.1 for narratives of these subjects.

In Trial CS8, more olezarsen-treated subjects developed treatment-emergent ADA compared to the placebo group (olezarsen 50 mg 41.4%; olezarsen 80 mg 40.4%; placebo 12.8%). Of the 125 subjects that were negative/unknown for ADA at baseline, 84 (67%) remained negative. In subjects who developed treatment-emergent ADAs, the median time to onset was 83 days in the olezarsen 50 mg group, 29 days in the olezarsen 80 mg group, and 169 days in the placebo group. The median duration for treatment-emergent ADA was 298 days, 281, and 84 days, in the olezarsen 50 mg, olezarsen 80 mg, and placebo groups, respectively.

Although there did not seem to be a clear association with ADA and AEs in either Trial CS3 or CS8, in the OLE CS13 study, there was a higher proportion of subjects with ADA that had ISRs and hypersensitivity events.

Conclusion

Treatment with olezarsen results in development of treatment-emergent ADA in approximately 40% of treated subjects. The incidence of ADA may increase with longer drug exposure as demonstrated in subjects that enrolled in the OLE study, CS13. Review of immunogenicity data from events during CS3 and CS8 did not demonstrate a clear relationship between AEs, including hypersensitivity events, and ADA status. In CS13, however, ISRs and hypersensitivity events were more frequent in subjects with treatment-emergent ADAs compared to subjects with ADA negative or treatment-unaffected status, although the numbers were small and therefore limit definitive causality assessments.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

No dedicated renal impairment study was conducted for olezarsen. The ultimate elimination of unconjugated olezarsen is likely a combination of slow nuclease metabolism within tissues and subsequent excretion of shortened metabolites (as well as any remaining full-length oligonucleotide) into urine.

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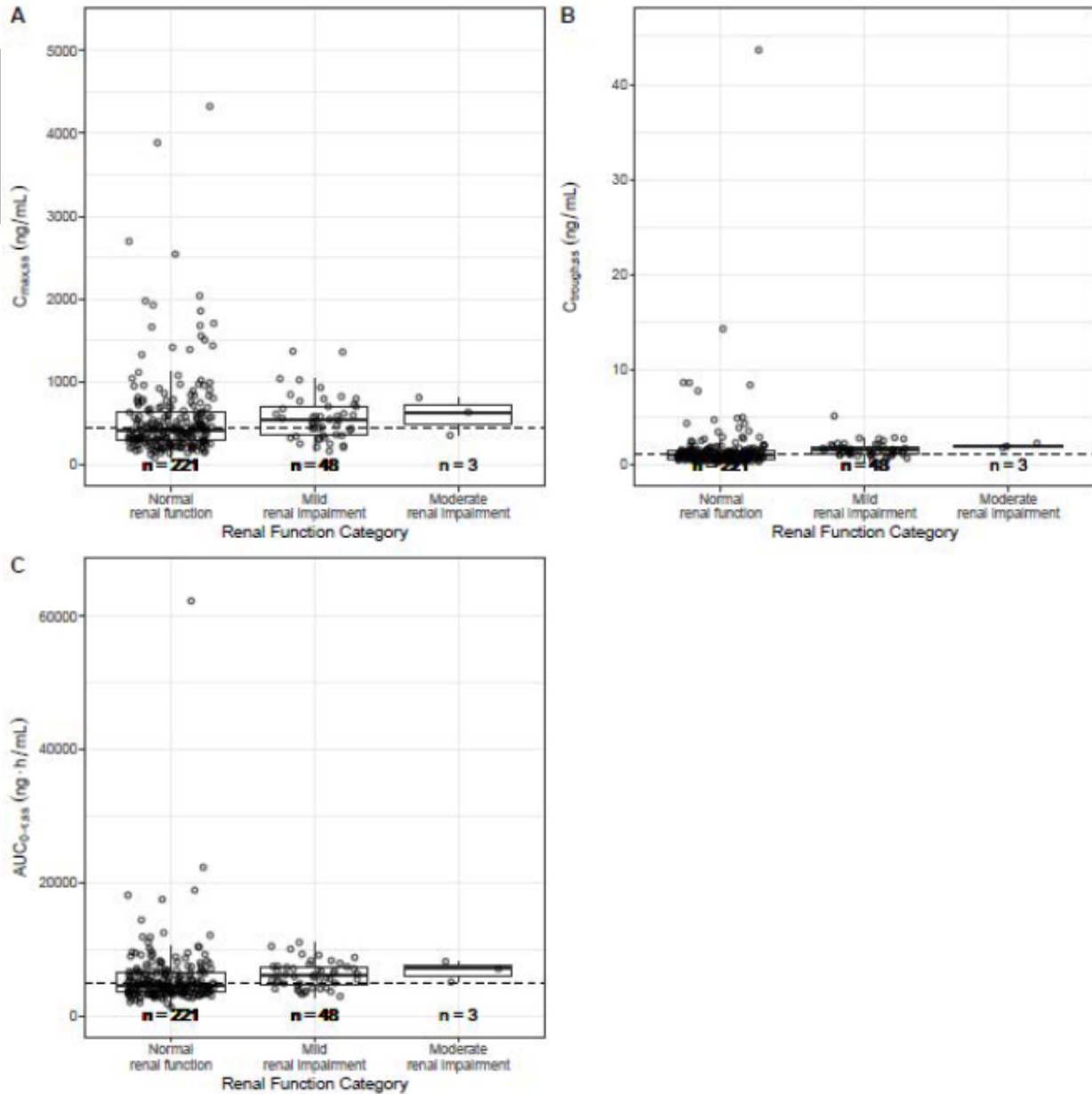
Tryngolza (olezarsen sodium)

Clinical studies conducted in this program enrolled participants with normal renal function as well as those with mild to moderate renal impairment. The range of post hoc estimates of steady-state exposure, including C_{max} , area under the concentration-time curve (AUC), and C_{trough} , were overlapping between participants with normal renal function (N=221) and participants with mild (N=48) or moderate (N=3) renal impairment ([Figure 32](#)). Consistent with PK exposure metrics, the range of post hoc estimates of steady-state percent change from baseline for ApoC-III and TG were overlapping between participants with normal renal function (N=219) and participants with mild (N=48) or moderate (N=3) renal impairment ([Figure 33](#) and [Figure 34](#)).

The review team agrees with the Applicant's labeling recommendation that no dose adjustment is needed in patients with mild or moderate renal impairment (≥ 30 mL/min).

Figure 32. Post Hoc Pharmacokinetic Metrics at Steady State vs. Covariates: Renal Function Category

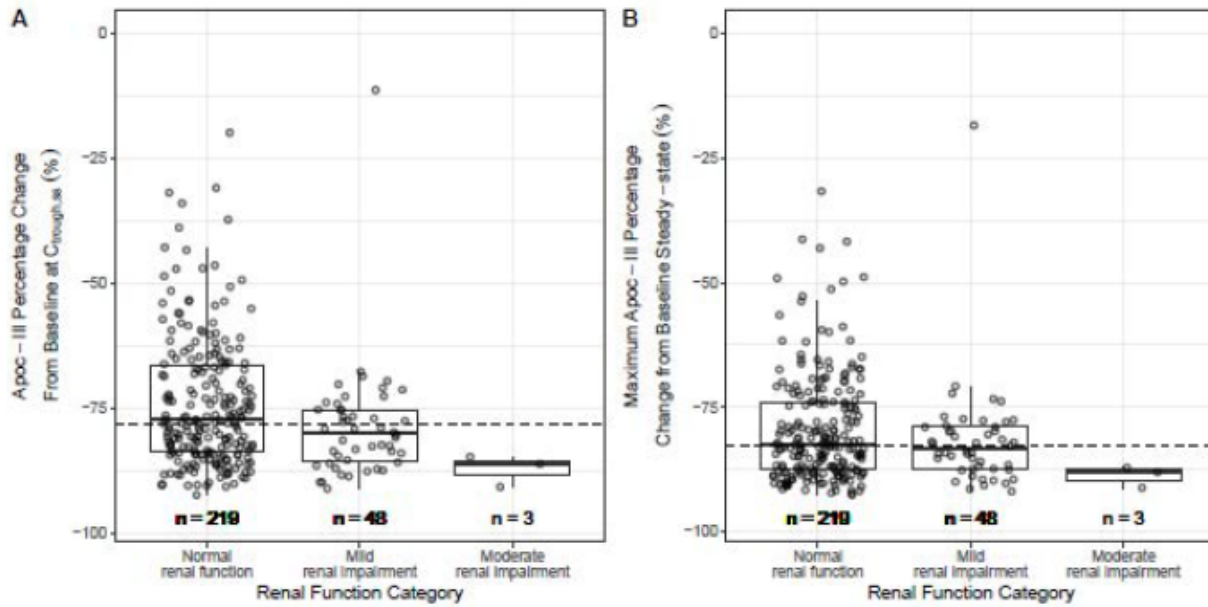
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Source: Figure 172 of 678354-ppk02-study-report

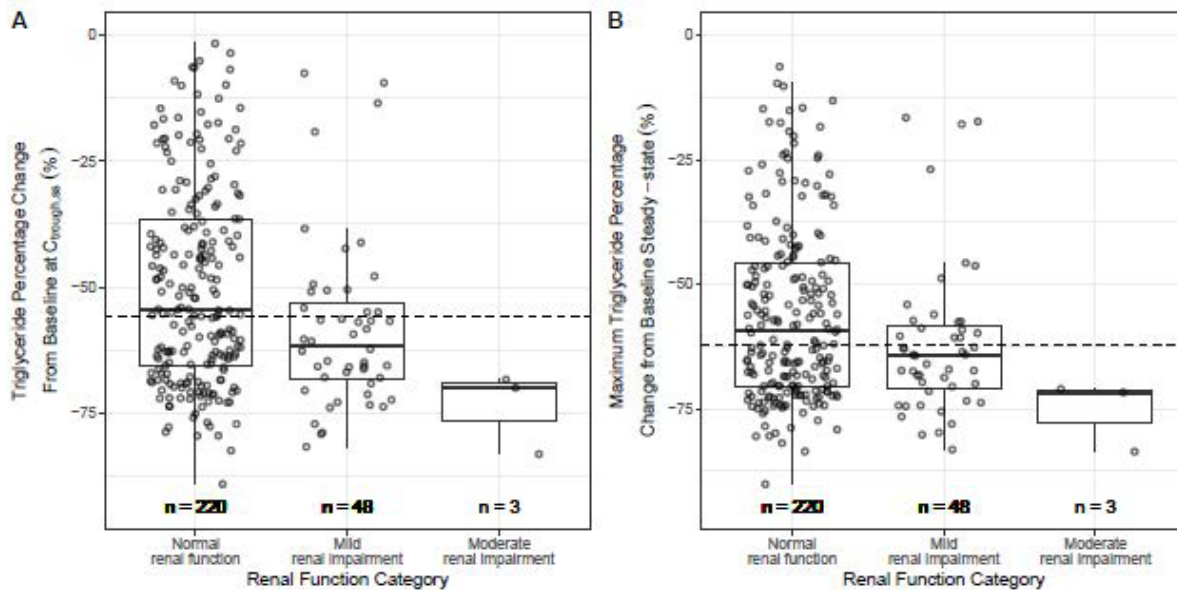
Abbreviations: AUC, area under the concentration-time curve; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state;

Figure 33. Post Hoc ApoC-III Metrics at Steady State vs. Covariates: Renal Function Category



Source: Figure 183 of 678354-ppk02-study-report
Abbreviations: apo, apolipoprotein; C_{trough,ss}, trough plasma concentration at steady state

Figure 34. Post Hoc Triglyceride Metrics at Steady State vs. Covariates: Renal Function Category



Source: Figure 194 of 678354-ppk02-study-report
Abbreviations: ApoC-III, apolipoprotein C-III; C_{trough,ss}, trough plasma concentration at steady state

APPEARS
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Hepatic Impairment

No dedicated hepatic impairment study was conducted for olezarsen. The Applicant has proposed the following language for use of olezarsen in patients with hepatic impairment (HI):

(b) (4)

Trials for olezarsen enrolled sixteen participants with mild HI based on the National Cancer Institute Organ Dysfunction Working Group criteria. Two subjects were from the healthy subject single ascending dose/multiple ascending dose study (ISIS 678354-CS1), one subject from healthy Japanese subject single ascending dose/multiple ascending dose study (ISIS AKCEA-CS1), six patients from dose-ranging study in patients with HTG and established or at high risk for CVD (ISIS 678354-CS2), four patients from confirmatory efficacy phase 2b study in patients with HTG (ISIS 678354-CS8) and three patients were from phase 3 study in patients with FCS (ISIS 678354-CS3 or Balance). One subject with moderate HI was enrolled in healthy subject study AKCEA-CS1. No patients with moderate or severe HI were enrolled in the studies.

The population PK analysis did not find baseline AST, ALT, or bilirubin as statistically significant covariates impacting olezarsen PK. Furthermore, the range of post hoc estimates of steady-state exposure, including C_{max} , AUC, and C_{trough} , were overlapping between participants with normal hepatic function (N=332) and participants with mild (N=16) or moderate (N=1) HI (based on National Cancer Institute Organ Dysfunction Working Group classification category) ([Figure 35](#)). Consistent with this, steady-state ApoC-III and TG reduction were similar between participants with normal hepatic function (N=330) and participants with mild (N=16) or moderate (N=1) HI ([Figure 36](#) & [Figure 37](#)).

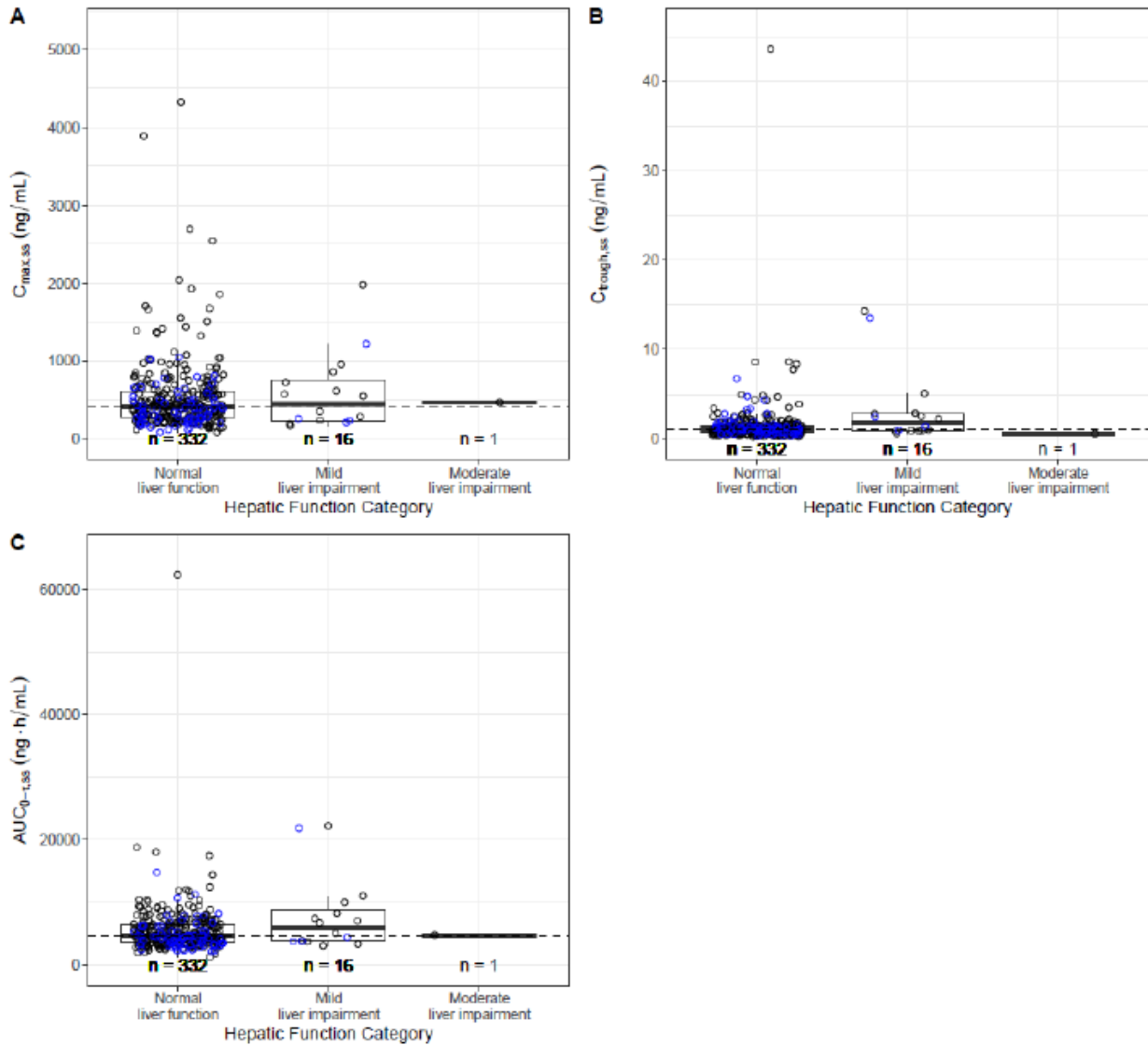
(b) (4)

The review team recommends

including the following labeling language:

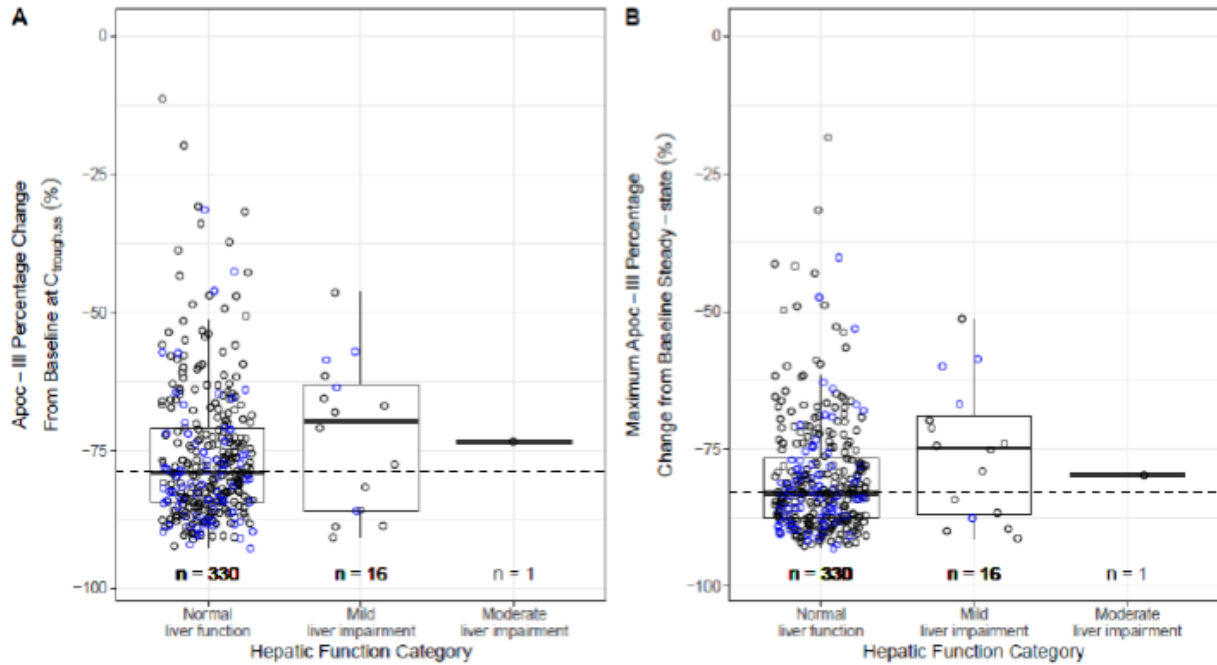
“No dose adjustment is (b) (4) in patients with mild hepatic impairment. TRYNGOLZA has not been studied in patients with moderate or severe hepatic impairment”.

Figure 35. Post Hoc Pharmacokinetic Metrics at Steady State vs. Covariates: Hepatic Dysfunction Category



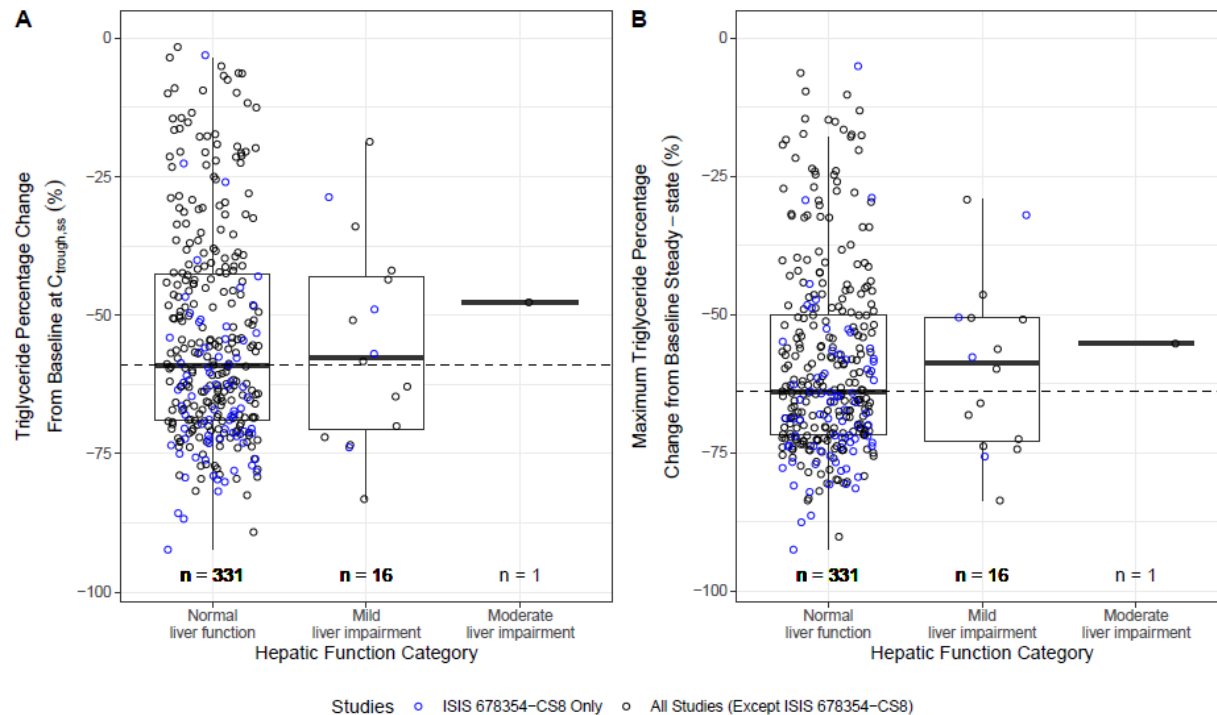
Source: Figure 1 of m1-11-3-clinical information amendment
Abbreviations: AUC, area under the concentration-time curve; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state

Figure 36. Post Hoc ApoC-III Metrics at Steady State vs. Covariates: Hepatic Dysfunction Category



Source: Figure 2 of m1-11-3-clinical information amendment
 Abbreviations: C_{trough,ss}, trough plasma concentration at steady state; apo, apolipoprotein

Figure 37. Post Hoc TG Metrics at Steady State vs. Covariates: Hepatic Dysfunction Category



Source: Figure 3 of m1-11-3-clinical information amendment
 Abbreviations: C_{trough,ss}, trough plasma concentration at steady state

Race

Japanese origin (from Study AKCEA-CS1) was identified as a statistically significant covariate on Vc/F in the population PK analysis. However, there were no clinically meaningful differences in olezarsen exposure metrics among categories of race (White, Black or African American, Asian, Japanese [from Study AKCEA-CS1], American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other or Unknown), given that exposures are still within the overall range of exposures seen in the population. The review team agrees that no dose adjustment is warranted on the basis of race.

Age and Sex

Age (adults aged <65 years [N=223], 65 to 74 years [N=41], and ≥75 years [N=8]) and sex were not identified as a statistically significant covariate in the population PK analysis. Slight differences in median $C_{max,ss}$ and $AUC_{tau,ss}$, are attributable to differences in body weight between male (median body weight 86.2 kg) and female participants (median body weight of 70.6 kg) and are not considered clinically meaningful, given that exposures are still within the overall range of exposures seen in the population. Therefore, no dose adjustment is required on the basis of age and sex.

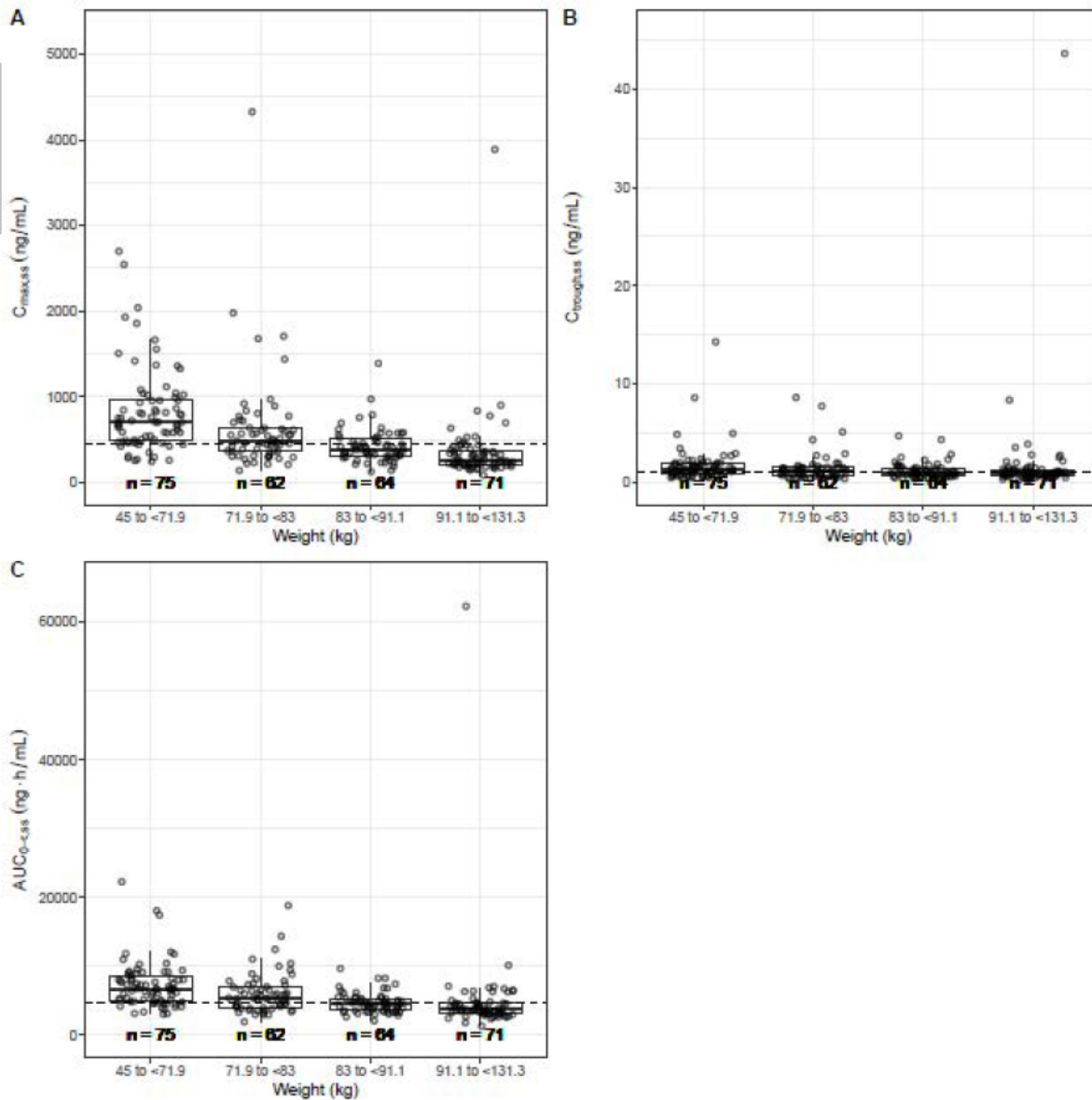
Body Weight

The population PK analysis identified body weight as a statistically significant covariate and as the most influential factor on olezarsen PK. Increased body weight was associated with increased apparent clearance (CL/F), Q/F, Vc/F, and Vp/F and k_a . Compared with a reference subject with a body weight of 70 kg, the median olezarsen exposure ($AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) for a participant at the 10th percentile of the body weight distribution, i.e., one with a weight of 61 kg, is expected to have a 16%, 28%, and 9% increase, respectively. A participant at the 90th percentile of the body weight distribution, i.e., one with a weight of 105 kg, is expected to have a 35% lower $AUC_{tau,ss}$, 55% lower $C_{max,ss}$, and 23% lower $C_{trough,ss}$ compared with a reference subject with weight of 70 kg. It is noted that the differences in $C_{trough,ss}$ between participants at the 10th and 90th percentiles of the body weight distribution were found to be smaller than the differences in $C_{max,ss}$ and $AUC_{tau,ss}$ for these participants.

A comparison of individual exposure metrics by body weight quartile was consistent with the magnitudes of differences found for the median exposure ([Figure 38](#)). While there was a trend of declining exposure with increasing body weight for $C_{max,ss}$ and $AUC_{tau,ss}$, no such apparent trend was identified for $C_{trough,ss}$. Consistent with the $C_{trough,ss}$, steady-state ApoC-III and TG reductions (percent change-from-baseline) were similar across different body weight groups.

The impact of body weight on olezarsen PK was, therefore, not considered clinically meaningful, and a fixed dose of 80 mg monthly is appropriate, regardless of body weight.

Figure 38. Post Hoc Pharmacokinetic Metrics at Steady State vs. Covariates: Body Weight



Source: Figure 171 of 678354-ppk02-study-report.

The horizontal dashed lines represent the median of the data across all categories.

Abbreviations: AUC, area under the concentration-time curve; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state

8.2. Extrinsic Factors

Drug Interactions

The drug-drug interaction potential of olezarsen involving cytochrome P450 (CYP) enzymes and human transporter proteins was investigated in vitro. Based on the in vitro evaluation, no clinically relevant drug-drug interactions are expected for olezarsen, and no drug-drug interaction-based dose adjustment is necessary.

Interaction With Highly Plasma Protein-Bound Drugs

No drug-drug interaction was observed in vitro with regard to plasma protein-binding displacement between olezarsen and highly plasma protein-bound drugs, warfarin, and ibuprofen in vitro, and thus olezarsen is not expected to have drug-drug interactions with highly plasma-bound drugs.

Metabolism and Transporter-Based Drug-Drug Interaction

Oligonucleotides like olezarsen are not substrates for the classic CYP metabolic pathways and thus their PK are unlikely to be impacted by other drugs that are CYP inhibitors or inducers. Olezarsen did not inhibit major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4). Olezarsen up to 10 µM did not induce CYP1A2, CYP2B6, or CYP3A4. At 10 and 100 µM, olezarsen was not a substrate or inhibitor, respectively, of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, bile salt export pump (BSEP), breast cancer resistance protein (BCRP), or P-gp. It is unlikely that olezarsen would impact the PK of compounds that are substrates of CYPs or transporters.

8.3. Plans for Pediatric Drug Development

Olezarsen was granted orphan drug designation for the FCS indication. The Applicant was exempt from the Pediatric Research Equity Act requirement. Olezarsen has not been studied in pediatric patients. The Applicant has an agreed Pediatric Investigation Plan with the European Medicine Agency that is deferred (b) (4) to determine pediatric dosing ([EMA 2023](#)).

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The Applicant conducted a fertility and early embryonic development study in male and female mice with olezarsen. The Agency agreed that embryofetal development and pre-/postnatal development evaluations conducted with the unconjugated active ASO component of olezarsen in mice and/or rabbits were adequate to support a marketing application.

[Table 86](#) summarizes the outcomes and conclusions of these studies. The identified multiples are based on a comparison of the BSA at the no observed adverse effect level (NOAEL) dose converted to a monthly dose relative to the monthly clinical dose of olezarsen, even though for some of the studies it was the unconjugated ASO that was administered. Regardless, as the unconjugated ASO is the active substance for both test articles administered, the comparison is considered acceptable. Refer to [Section 13](#) for further details of the reproductive toxicity studies conducted with the conjugated and unconjugated ASO. Specific labelling recommendations will be addressed separately.

Table 86. Nonclinical Data Supporting Labelling for Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Combined fertility and embryo-fetal development study in mice with the unconjugated (lacking GalNAc) ASO. • Unconjugated ASO administered to male and female mice by subcutaneous injection at doses of 3, 10, or 25 mg/kg every other day (10.5, 35, and 87.5 mg/kg/wk) prior to mating and through the completion of organogenesis on gestation day 15 • No adverse developmental outcomes were noted at doses up to 87.5 mg/kg/wk (highest dose administered) • Low concentrations of the unconjugated ASO were measurable in placental tissue (<10% of maternal plasma levels) while levels in fetal tissue were below the limit of detection • The NOAEL was 87.5 mg/kg/wk (approximately 21x the MRHD based on BSA comparison of the unconjugated ASO) Embryo-fetal development study in pregnant rabbits with the unconjugated ASO. • Unconjugated ASO administered by subcutaneous injection at doses of 3, 6, or 15 mg/kg every other day (10.5, 21, and 52.5 mg/kg/wk) during the period of organogenesis on gestation days 6 to 18 • A maternally toxic dose of 52.5 mg/kg/wk was associated with abortions and early delivery but was not associated with adverse developmental outcomes • Low concentrations of the unconjugated ASO were measurable in placental tissue (~7% of maternal plasma levels), whereas levels in fetal tissue were below the limit of detection • The NOAEL was mid dose of 21 mg/kg/wk (approximately 20x the MRHD based on BSA comparison of the unconjugated ASO) Pre- and postnatal study in mice with the unconjugated ASO. • Unconjugated ASO administered to dams by subcutaneous injection at doses of 3, 10, or 25 mg/kg every other day (10.5, 35, and 87.5 mg/kg/wk) from gestation day 6 through lactation day 21 (weaning) • Decreases in offspring body weights were associated with delays in the development of morphological landmarks at 87.5 mg/kg/wk • The maternal NOAEL was the high dose of 87.5 mg/kg/wk (approximately 21x the MRHD based on comparison of the active substance dose). The NOAEL for effects on offspring was the mid dose of 105 mg/kg/wk, (approximately 9x the MRHD based on BSA comparison of the unconjugated ASO).
8.2 Lactation	• In milk from lactating mice from the pre- and postnatal toxicity study given subcutaneous doses of the unconjugated ASO at 87.5 mg/kg/wk, very low levels (<0.01% of maternal liver levels) were detected.

Labeling Section	Nonclinical Data
13.1 Impairment of Fertility	- Olezarsen was administered every other week to males for 14 weeks and every other week to females prior to mating followed by every other day after mating until gestation day 6 at doses of 0, 5, 10, or 20 mg/kg. - No effect on fertility in mice administered olezarsen at doses up to 20 mg/kg every other week (approximately 2 times the clinical dose based on BSA comparison).

Source: Reviewer-generated table.

Abbreviations: ASO, antisense oligonucleotide; BSA, body surface area; GalNAc, N-acetyl galactosamine; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; wk, week(s)

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 218614 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective. As part of this action, an expiration period of 36 months for the product, stored under refrigerated condition at 2°C to 8°C (36°F to 46°F) in the commercial packaging, is granted.

9.1. Device or Combination Product Considerations

As supported by the following information, the proposed Tryngolza (olezarsen) 80 mg/0.8 mL auto-injector can be approved.

1. The Center for Devices and Radiological Health review team concluded that the components of the autoinjector, its engineering design, and functionality are adequate and that the device constituent parts of this combination product are approvable (refer to the review by Dr. Akm Khairuzzaman in DARRTS under NDA 218614, dated October 9, 2024; Reference ID: 5460215).
2. The Human Factors team has concluded that the Applicant does not need to submit Human Factors validation results with their marketing application for the proposed Tryngolza (olezarsen) injection, 80 mg/0.8 mL auto-injector as an identical version was reviewed previously under their olezarsen IND 136692 (refer to the review by Drs. Konkani and

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Tryngolza (olezarsen sodium)

Oguntimein in DARRTS under NDA 218614, dated August 13, 2024; Reference ID: 5428868)^{6,7,8}.

3. The clinical pharmacology team has determined that the BE study ISIS 678354-CS20, in conjunction with the exposure-response analyses for efficacy and safety, support that intended commercial 80 mg olezarsen administered as a 100 mg/mL formulation via autoinjector is therapeutically equivalent to 80 mg olezarsen administered as a 100 mg/mL formulation via vial with syringe, as used in the clinical program (see Section [6.1](#) for details).

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Human Subjects Protections

According to the Applicant, the clinical trials were conducted in substantial conformance with International Council for Harmonization good clinical practice requirements and with applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research.

Clinical Site Inspections

Two clinical investigator inspections (CIs) were conducted and the Contract Research Organization (CRO) Medpace was inspected for the submitted trials. The inspection of one site for CS8 found two unreported AEs (redness at the injection site and nausea) in two subjects, both in olezarsen 80 mg group. This CI also enrolled three ineligible subjects in CS8, which were reported to the FDA as protocol deviations.

Based on the overall inspection results of these CIs, CRO, and the regulatory assessments, the data generated by the CIs, managed by the CRO, and submitted by the Applicant are verifiable. Trials ISIS 678354-CS3 and ISIS 678354-CS8 appear to have been conducted adequately and the clinical data submitted by the Applicant appear acceptable in support of the respective indication. See Section [22](#).

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators* and by 21 CFR 54.4 ([February 2013a](#)). None of the investigators of the pivotal and confirmatory trials

⁶ Konkani. A. Use-Related Risk Analysis and Comparative Analyses review for ISIS 678354 (olezarsen) injection, (b) (4) 80 mg/0.8 mL AI. (IND 136692). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 09 April 2024. TTT No.: 2022-2622.

⁷ Konkani. A. Use-Related Risk Analysis and Comparative Analyses review for ISIS 678354 (olezarsen) injection, (b) (4) 80 mg/0.8 mL AI. (IND 136692). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 09 April 2024. TTT No.: 2022-2622.

⁸ NDA 218614 Response to Information Request. Carlbab (CA): Ionis Pharmaceuticals, Inc. 2024 JUL 24. Available from: \\CDSESUB1\EVSPROD\nda218614\0014\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\fcs\5354-other-stud-rep\hfe-ue\human-factor-autoinjector-report.pdf

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(CS3 and CS8) were employed by the Applicant, and none disclosed financial interests with the Applicant. In conclusion, the likelihood that the trial results were biased on financial interests is minimal and should not affect the approvability of the application. See Section [25](#).

11. Advisory Committee Summary

An advisory committee meeting was not convened for this application.

The application for the related drug volanesorsen for treatment of FCS was discussed at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on May 10, 2018. The committee voted 12 to 8 in favor of approval.

The primary safety risk for volanesorsen was severe thrombocytopenia.

Olezarsen has the same nucleotide sequence and backbone chemical composition as volanesorsen and differs from it only through its inclusion of triantennary N-acetyl galactosamine (GalNAc3), which allows for lower dosing and injection volume than with volanesorsen.

The safety and effectiveness concerns with volanesorsen have been largely addressed or resolved with the olezarsen product. Olezarsen has a mild signal for thrombocytopenia but not a signal for bleeding. Olezarsen 80 mg statistically significantly reduces TG to a clinically meaningful degree. In Study CS3, for the total olezarsen group (80 mg + 50 mg groups), a decrease in the adjudicated pancreatitis event rate was observed compared with placebo. Safety concerns with olezarsen are monitorable and can be addressed in labeling. These issues do not rise to the level of requiring advisory committee input.

III. Additional Analyses and Information

12. Summary of Regulatory History

ISIS 678354 (also referred to as olezarsen) is being developed for treatment of familial chylomicronemia syndrome (FCS).

Notable Regulatory Milestones

On December 14, 2017, the initial IND 136692 for olezarsen was submitted (b) (4)

After review, the trial was determined safe to proceed and FDA issued non-hold clinical and nonclinical comments in an advice/information request letter on January 16, 2018.

On December 22, 2022, a request for Fast Track designation for the treatment of FCS was submitted. On January 19, 2023, the Fast Track designation was granted for olezarsen to reduce triglycerides (TG) in adults with FCS.

On September 13, 2023, a request for review of the proposed proprietary name Tryngolza was submitted to IND 136692. On March 11, 2024, a Proprietary Name Request Conditionally Acceptable letter was issued for Tryngolza.

On January 18, 2024, a request for Breakthrough Therapy designation was submitted for the treatment of FCS. The Breakthrough Therapy designation was granted on February 20, 2024, for use of olezarsen as an adjunct to diet to reduce TG in patients with FCS.

On February 14, 2024, orphan drug designation was granted for olezarsen for treatment of FCS.

On April 19, 2024, the original NDA 218614 for olezarsen was submitted for the proposed indication:

As an adjunct to diet to reduce triglycerides in adults with FCS.

On June 18, 2024, the application was filed, and the Filing Communication was issued conveying no filing review issues were identified and the Applicant was notified that the application received priority review.

Milestone Meetings

On September 1, 2017, the pre-investigational new drug application file 136692 was opened for olezarsen with the submission of a Type B pre-investigational new drug meeting request. The purpose of this meeting was to discuss the adequacy of nonclinical and clinical development plans to support an IND (b) (4)

Written Responses were issued on October 31, 2017.

On April 17, 2020, a Type B End-of-Phase 2 (EOP2) meeting was requested to discuss the development plan for treatment of FCS. On April 28, 2020, a Meeting Granted letter was issued informing the Applicant that an EOP2 meeting request was premature and that Type C Written

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Responses would be issued in lieu of a meeting. The May 15, 2020, meeting package contained a protocol for Trial ISIS 678354-CS3, titled, *A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRX (ISIS 678354) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)*. The FDA informed the Applicant that we had several concerns about the adequacy of this program to enter phase 3 development and that we were providing general preliminary comments on the planned phase 3 program and recommendations for obtaining additional data. The Written Responses were issued on July 1, 2020.

On December 7, 2021, a Type C meeting was requested to discuss the proposed bioequivalence (BE) study (protocol number ISIS 678354-CS20, titled, *A “Single Dose”, Randomized, Open-Label, Two-Period Crossover, Bioequivalence Study Comparing Two Subcutaneous Formulations: Vial and Autoinjector (AI) with Olezarsen, at Two Dose Levels, in Healthy Adult Participants*) to transition from the currently used vial drug product to an AI presentation. On December 17, 2021, a Meeting Request Granted Written Responses Only letter was issued. The FDA informed the Applicant that we did not agree on the proposed design for the BE Study ISIS 678354-CS20, we did not agree with the Applicant’s rationale for bridging the 50 mg and 80 mg doses, and we did not agree that the overall bridging strategy was adequate to support NDA filing with the AI configuration. The Written Responses also included additional Chemistry, Manufacturing, and Controls, device, and combination product comments from the FDA. The Written Responses were issued on February 16, 2022.

On April 5, 2022, a Type C meeting was requested to discuss the proposed safety database to support an NDA submission. On April 26, 2022, a teleconference was granted and scheduled for June 13, 2022. The April 26, 2022, Meeting Granted letter contained a request for the background package to include additional information on how the Applicant intended to demonstrate substantial evidence of effectiveness to support an indication in FCS and the overall clinical pharmacology package, including plans regarding assessment of the effect of hepatic impairment, the bridging of the autoinjector, and addressing QT-IRT comments. The Preliminary Comments were issued on July 29, 2022. Relevant issues discussed at the meeting, and reflected in the August 9, 2022, Meeting Minutes, are reflected below:

1. The Applicant’s agreement to submit final results of Trial 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, at the time an ongoing trial studying severe and moderate hypertriglyceridemia*), (b) (4).
2. The Applicant agreed to revise the BE study and use AUC_{0-336h} instead of (b) (4) as the pharmacokinetics (PK) endpoint to account for $\geq 85\%$ of AUC_{0-inf} .
3. Agreement that CS8, in addition to CS3, could serve as confirmatory evidence for the FCS indication.

On March 30, 2023, a Type C meeting was requested to discuss the proposed integrated analysis plan and submission contents for the FCS NDA. On June 7, 2023, the Written Responses were issued and included recommendations for pooling strategies as the FDA informed the Applicant that we did not agree with the proposed pooling strategy. The FDA agreed that an Integrated Summary of Efficacy would not need to be included in the NDA submission. The FDA also

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provided comment on the content of clinical trial and nonclinical study data to be provided in the NDA submission.

On September 27, 2023, a Pre-NDA meeting was requested, and the meeting was granted and scheduled for December 12, 2023. On December 6, 2023, the Preliminary Comments were issued and included FDA comments on the content and format of the FCS NDA submission. The Applicant found the Preliminary Comments acceptable and canceled the meeting.

On October 31, 2023, the Applicant requested a Type D meeting to discuss drug product shelf life. The FDA informed the Applicant that we did not agree with their:

1.  (b) (4)
2. 

Written Responses were issued on December 15, 2023.

Pediatric Research Equity Act

Because olezarsen for this indication was granted orphan drug designation, the Applicant was exempt from the Pediatric Research Equity Act requirement.

 (b) (4)

13. Pharmacology Toxicology

Olezarsen (ISIS 678354) and/or volanesorsen (GalNAc-unconjugated form of olezarsen) were characterized in a series of nonclinical pharmacology, pharmacokinetic, and toxicology studies. The pharmacologic activity of olezarsen was evaluated in a series of *in vitro* and *in vivo* studies, receptor binding activity was evaluated in a secondary pharmacology study, and safety pharmacology studies were evaluated in cell lines and in cynomolgus monkeys.

The absorption, distribution, metabolism, and excretion profile was primarily characterized as a component of the repeat-dose toxicity studies. Additionally, a series of single dose studies were also performed in rats at various ages, in achondroplastic and wild-type mice, and by various routes of administration.

The toxicity profile was established in a series of *in vitro* and *in vivo* studies. Repeat-dose toxicity, fertility and early embryonic development, and genotoxicity were conducted with olezarsen, while carcinogenicity, embryofetal development, and pre-/postnatal development were evaluated in studies with volanesorsen, the unconjugated active antisense oligonucleotide (ASO). The mRNA sequence to which the ASO hybridizes is identical between humans and non-human primates (NHPs) but differs in rodents. For this reason, the Applicant used human *apoC-III*

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transgenic mice to evaluate pharmacologic effects and included groups administered species-specific ASOs in many of the pivotal tox studies conducted in rodents.

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Not applicable.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable.

13.3. Review of Studies Supporting the New Drug Application

13.3.1. Pharmacology

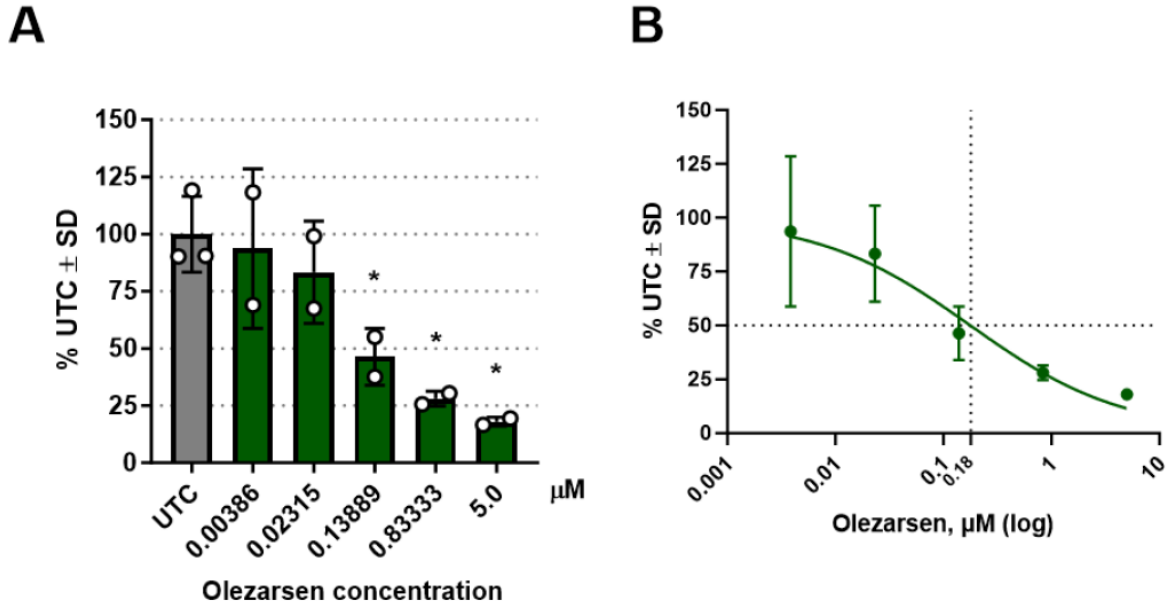
Pharmacology

The Applicant conducted both in vitro and in vivo studies to demonstrate pharmacological activity with olezarsen. Activity was characterized in vitro using primary hepatocytes (human and transgenic mouse) and in vivo activity was demonstrated in wild-type mice, transgenic mice expressing human *apoC-III*, and in NHPs (cynomolgus monkeys). Results from the in vitro pharmacology studies demonstrated that olezarsen reduces *apoC-III* mRNA up to 89% compared to untreated controls. Results from the in vivo studies demonstrated dose- and time-dependent reductions of liver *apoC-III* mRNA, plasma ApoC-III protein and plasma TG levels. These effects were consistent with the expected pharmacological properties of the compound. Results from these animal models showed reasonable proof-of-concept and included a clinically translatable endpoint (plasma TG). Key observations from studies demonstrating pharmacologic activity are summarized below.

In Vitro Pharmacological Activity of ISIS 678354 in Primary Human Hepatocytes

In a study (Study No. 20-1d52) in primary human hepatocytes (HepatoPac®), olezarsen produced a concentration-dependent reduction of ApoC-III protein with a half-maximal inhibitory concentration (IC₅₀) of 0.18 μM and maximal efficacy of 82% knockdown in *apoC-III* mRNA levels after 48 hours of incubation followed by 48 hours of recovery. See [Figure 39](#) below.

Figure 39. Concentration-Dependent Reductions of *apoC-III* mRNA in HepatoPac® Cells Treated With ISIS 678354



Source: Figure 2 of Sponsor's pharmacology written summary

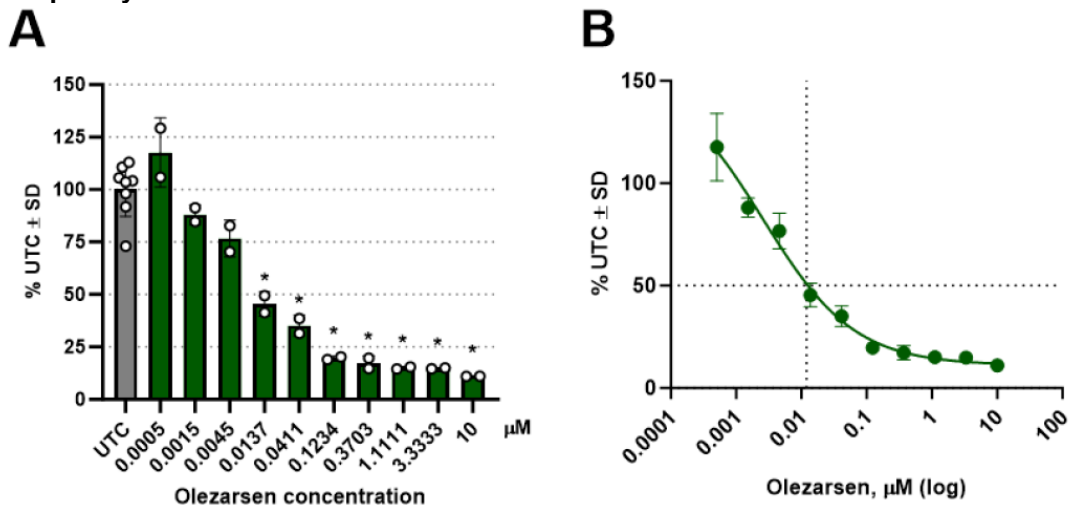
(A) Bar graph represents the mean percentage difference between the untreated controls (UTC) $\pm$ standard deviation (SD) at each dose tested. * $P < 0.05$ vs UTC. (B) Dose response curve of mean percentage difference from UTC $\pm$ SD at each tested dose.

Abbreviations: apo, apolipoprotein; SD, standard deviation; UTC, untreated control

In Vitro Pharmacological Activity of ISIS 678354 in Primary Transgenic Hepatocytes

In a study (Study No. 23-Of53, 20-190a) conducted with transgenic mouse hepatocytes expressing human *apoC-III* gene, olezarsen produced a concentration-dependent reduction of *apoC-III* mRNA with an IC_{50} of 0.012 μM and maximal efficacy of 89% knockdown in *apoC-III* mRNA levels following overnight incubation with olezarsen. See [Figure 40](#) below.

Figure 40. Concentration-Dependent Reduction of Human *apoC-III* mRNA in Primary Transgenic Mouse Hepatocytes Treated With ISIS 678354



Source: Figure 3 of Applicant's pharmacology written summary.
(A) The mean percentage difference from the UTC ± SD at each dose tested. (B) Dose response curve of mean percentage difference from UTC ± SD at each tested dose.
Abbreviations: apo, apolipoprotein; SD, standard deviation; UTC, untreated control

Dose Response Evaluation of ISIS 838707 in Wild-Type Mice Fed a Normal Chow Diet

An in vivo study (Study No. EX/3980_166) was conducted in wild-type CD-1 mice using a mouse-specific surrogate ApoC-III ASO (ISIS 838707, a murine GalNac3-conjugated version of olezarsen) because olezarsen is not pharmacologically active in mice due to the divergence in sequence between mouse and human ApoC-III protein.

CD-1 mice were injected once weekly by subcutaneous (SC) injection with ISIS 838707 (5 and 10 mg/kg/week or saline) for 6 weeks. Forty-eight hours following the last treatment, a dose-related reduction in liver *apoC-III* mRNA expression and plasma TG levels were noted, with the reductions reaching 88% and 76%, respectively, compared to untreated control mice at the 10 mg/kg/wk dose. See [Table 87](#) below.

Table 87. Dose-Dependent Reductions in Murine *apoC-III* mRNA and Plasma TG Levels in Wild-Type CD-1 Mice After 6 Weeks Subcutaneous Administration of ISIS 838707

WT CD-1 (Chow)	Saline	ISIS 838707 (10 mg/kg/wk), % saline	ISIS 838707 (5 mg/kg/wk), % saline
Liver ApoC-III	100 ± 8	12 ± 7 [#]	19 ± 11 [#]
Plasma TG	100 ± 34	24 ± 9 [#]	36 ± 11 [#]

[#] Statistically significant ($p < 0.05$) compared to saline control; data are expressed as mean percent of saline ± SD. Mouse *apoC-III* liver mRNA and plasma triglycerides (TG) were measured 48 hrs after 6 weeks ISIS 838707 (a GalNac conjugated ASO that selectively targets mouse apoC-III) 10 and 5 mg/kg/wk, or saline (N = 4/group). Dosing was performed by SC injection.

Source: Table 4 of Applicant's pharmacology written summary
Abbreviations: apo, apolipoprotein; GalNac, N-acetyl galactosamine; SC, subcutaneous; SD, standard deviation; TG, triglycerides; wk, week(s); WT, wild-type

Dose Response Evaluation of ISIS 678354 in Human *apoC-III* Transgenic mice

An in vivo study (study No. EX/3979_73, 23-144a) was conducted in transgenic mice that express human *apoC-III* gene and have extremely high levels of TG. Human *apoC-III* transgenic mice treated with a single dose of olezarsen at 0.3, 1, 3, and 10 mg/kg showed dose-dependent reductions in liver *apoC-III* mRNA by up to 77% and plasma ApoC-III protein and plasma TG with up to 87% reduction in liver *apoC-III* mRNA and plasma TG at the 10 mg/kg dose (see [Table 88](#) below). The median effective dose (ED₅₀) values for liver ApoC-III, plasma ApoC-III, and plasma TG reductions were identified as 1.3, 0.8, and 0.9 mg/kg, respectively.

Table 88. Dose-Responsive Effect of ISIS 678354 Treatment on Liver *apoC-III* mRNA, Plasma ApoC-III Protein, and Plasma TG in Human ApoC-III Transgenic Mice

Group	Dose, mg/kg	Liver ApoC-III, % saline	Baseline plasma ApoC-III, mg/dL	Plasma ApoC-III, % baseline	Baseline plasma TG, mg/dL	Plasma TG, % baseline
Saline	N/A	100 ± 25	109 ± 37	86 ± 3	2,015 ± 109	99 ± 7
Olezarsen	10	23 ± 3 [#]	172 ± 27	13 ± 1 [#]	3,404 ± 172	13 ± 3 [#]
Olezarsen	3	26 ± 2 [#]	138 ± 19	22 ± 1 [#]	2,588 ± 138	21 ± 2 [#]
Olezarsen	1	46 ± 11 [#]	118 ± 47	45 ± 6 [#]	2,616 ± 118	40 ± 14 [#]
Olezarsen	0.3	97 ± 15	127 ± 34	72 ± 6	2,412 ± 127	82 ± 20

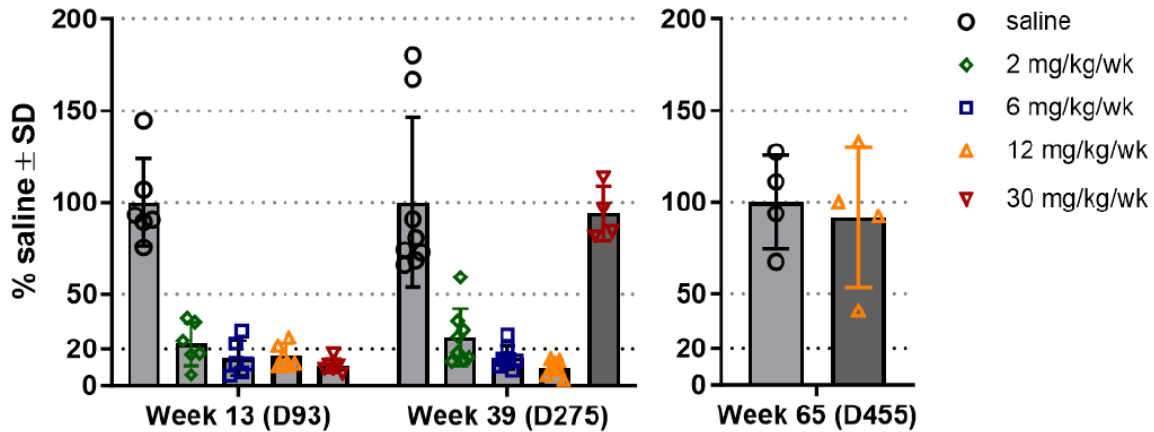
[#] Statistically significant ($p < 0.05$) compared to control; data are expressed as mean percent of saline or baseline value ± SD. Human *apoC-III* liver mRNA, human *apoC-III* plasma protein and plasma TG were measured 72 hrs after a single administration of saline or 10, 3, 1 and 0.3 mg/kg olezarsen (N = 4/group for saline; N = 3/group for olezarsen groups). Dosing was performed by subcutaneous (SC) injection. Mean values ± standard deviation (SD) are shown as a percent of saline control for liver *apoC-III* and as a percentage of an animal's baseline value for plasma *apoC-III* and plasma TG. Baseline plasma *apoC-III* and plasma TG demonstrate the extent of severe hypertriglyceridemia in this mouse model.

Source: Adapted from Table 3 of Applicant's Pharmacology Written Summary
Abbreviations: apo, apolipoprotein; GalNAc, N-acetyl galactosamine; N/A, not applicable; SC, subcutaneous; SD, standard deviation; TG, triglycerides

Dose Response Evaluation of ISIS 678354 in 39-Week Study in Lean Cynomolgus Monkeys

Non-human primates (cynomolgus monkeys) are considered the most relevant nonclinical species because the pharmacologically active ASO portion of olezarsen exhibits full complementarity to the human *apoC-III* mRNA transcript sequence. Cynomolgus monkeys were administered olezarsen SC at 2, 6, 12, and 30 mg/kg/wk, once weekly for up to 39 weeks in a toxicology study (study No. 678354 – AS02) that included recovery assessments following 13- or 39-weeks of treatment. Regarding pharmacologic endpoints, there were dose-dependent reductions in liver *apoC-III* mRNA up to 90% and plasma *apoC-III* mRNA up to 77% compared to pre-dose that were maintained for the duration of treatment. A reversal of these effects was seen following recovery periods (see [Figure 41](#) and [Table 89](#) below). Minimal effects on plasma TG levels were noted since chow-fed cynomolgus monkeys already have very low plasma TG levels (<50 mg/dL).

Figure 41. Liver ApoC-III Expression Following 2, 6, 12, and 30 mg/kg/wk ISIS 678354 (Olezarsen) Treatment in Cynomolgus Monkeys After 13- and 39-Week Treatment Period With a 26-Week Recovery Period in the 12 and 30 mg/kg/wk Groups



Cynomolgus monkey apoC-III liver mRNA was measured after 13 and 39 weeks of weekly SC administration of olezarsen at 2, 6, 12, and 30 mg/kg/wk, or the vehicle saline. Liver apoC-III recovery following cessation of dosing was evaluated in the 12 and 30 mg/kg/wk cohorts as follows: in the 12 mg/kg/wk group, a cohort of animals were dosed 39 weeks and then allowed 26 weeks of recovery (Week 65 or Day 455 recovery time point). Within the 30 mg/kg/wk group, a cohort of animals were dosed 13 weeks and then allowed 26 weeks of recovery (Week 39 or Day 275 recovery time point).

Source: Adapted from Figure 7 of Applicant's pharmacology written summary
Abbreviations: apo, apolipoprotein; D, day; SC, subcutaneous; SD, standard deviation; wk, week(s)

Table 89. Plasma ApoC-III Levels Following 2, 6, 12, and 30 mg/kg/wk ISIS 678314 (Olezarsen) Treatment in Cynomolgus Monkeys Over a 39-Week (Day 275) Treatment Period With a 26-Week Recovery Period in the 30 mg/kg/week Group

	Pre-dose	Day 44 (Week 6)	Day 93 (Week 13)	Day 184 (Week 26)	Day 275 (Week 39)
Saline	100 ± 12	110 ± 15	118 ± 13	130 ± 12	148 ± 14
2 mg/kg/wk	100 ± 23	44 ± 11 [#]	47 ± 11 [#]	50 ± 10	55 ± 7
6 mg/kg/wk	100 ± 20	13 ± 6 [#]	45 ± 9 [#]	23 ± 9 [#]	45 ± 12 [#]
12 mg/kg/wk	100 ± 16	20 ± 6 [#]	31 ± 9 [#]	40 ± 7 [#]	40 ± 5 [#]
30 mg/kg/wk	100 ± 13	6 ± 4 [#]	12 ± 5 [#]	44 ± 9 [#] (recovery from Week 13 dose)	96 ± 18 (recovery from Week 13 dose)

[#] Statistically significant ($p < 0.05$) compared to pre-dose of each group; two-way ANOVA, Dunnett's multiple comparison test. Data are expressed as percent of group baseline value ± SEM.

Source: Adapted from Table 6 of Applicant's Pharmacology Written Summary
Abbreviations: ANOVA, analysis of variance; apo, apolipoprotein; SEM, standard error of the mean; wk, week(s)

Safety Pharmacology

Safety pharmacology endpoints were evaluated in a series of in vitro and in vivo assays (see [Table 90](#)).

Table 90. Safety Pharmacology Studies

Study/ Study No.	Key Findings/Relevance
Effect of Olezarsen on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (study 678354-IS05)	At concentrations of 30 and 300 μM , minimal reductions (<2%) in hERG current were noted. The IC_{50} was considered >300 μM (greater than 1000 times the human exposure).
Evaluation of Cardiovascular, Respiratory, and Central Nervous Systems Following Subcutaneous Administration of Olezarsen in Cynomolgus Monkeys (study 678354-AS03)	Single subcutaneous doses of 0, 12, or 30 mg/kg were administered to male monkeys in an ascending dose paradigm with a 1-week washout period between doses. Respiratory and cardiovascular endpoints were evaluated in one cohort of animals (4/group) while CNS endpoints were evaluated in a second cohort (4/group). Other than a transient increase in heart rate at the highest dose at 360 minutes, there were no effects on cardiovascular, respiratory, or central nervous system functioning observed.

Source: Reviewer-generated table.

Abbreviations: CNS, central nervous system; IC_{50} , half maximal inhibitory concentration

Secondary Pharmacology

In a battery of secondary pharmacology assays (in vitro assays and in silico assays), olezarsen was evaluated for induction or inhibition of cytochrome P450 and as an inhibitor or substrate for various transporters (see [Table 91](#) below).

Table 91. Secondary Pharmacology Studies

Study/ Study No.	Key Findings/Relevance
In Vitro Assessment of Cytochrome P450 Induction Potential of ISIS 678354 in Plated Cryopreserved Human Primary Hepatocytes (study 678354-IS07)	Olezarsen at concentrations up to 50 μM in two donors and up to 10 μM in one donor, did not cause significant induction of the enzymes CYP1A2, CYP2B6, or CYP3A4 at either the mRNA level or enzyme activity level in the cryopreserved primary human hepatocytes. Therefore, olezarsen has a low potential for involvement in cytochrome p450 drug-drug interactions.
Cellular Uptake and In Vitro Evaluation of ISIS 678354 as Inhibitors of Cytochrome P450 Expression in Human Hepatocytes (study 678354-IS10)	Olezarsen at concentrations up to 50 μM did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Therefore, olezarsen has a low potential for involvement in cytochrome p450 drug-drug interactions.
Assessment of ISIS 678354 as an inhibitor or a substrate of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP mediated transport (study 678354-IS08)	Olezarsen at concentrations of 10 μM and 100 μM was not a substrate or inhibitor of the drug transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP. Therefore, olezarsen has a low potential for involvement in transporter drug-drug interactions.

Source: Reviewer-generated table.

Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CYP, cytochrome P450; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein

13.3.2. Absorption, Distribution, Metabolism, and Excretion/Pharmacokinetics

The nonclinical pharmacokinetic and toxicokinetic (PK/TK) parameters of olezarsen, including absorption, distribution, metabolism, and excretion, were characterized in the mouse following single and repeat SC dosing in 6-, 13-, and 26-week studies, and in monkeys following repeat-dosing in the 39-week study.

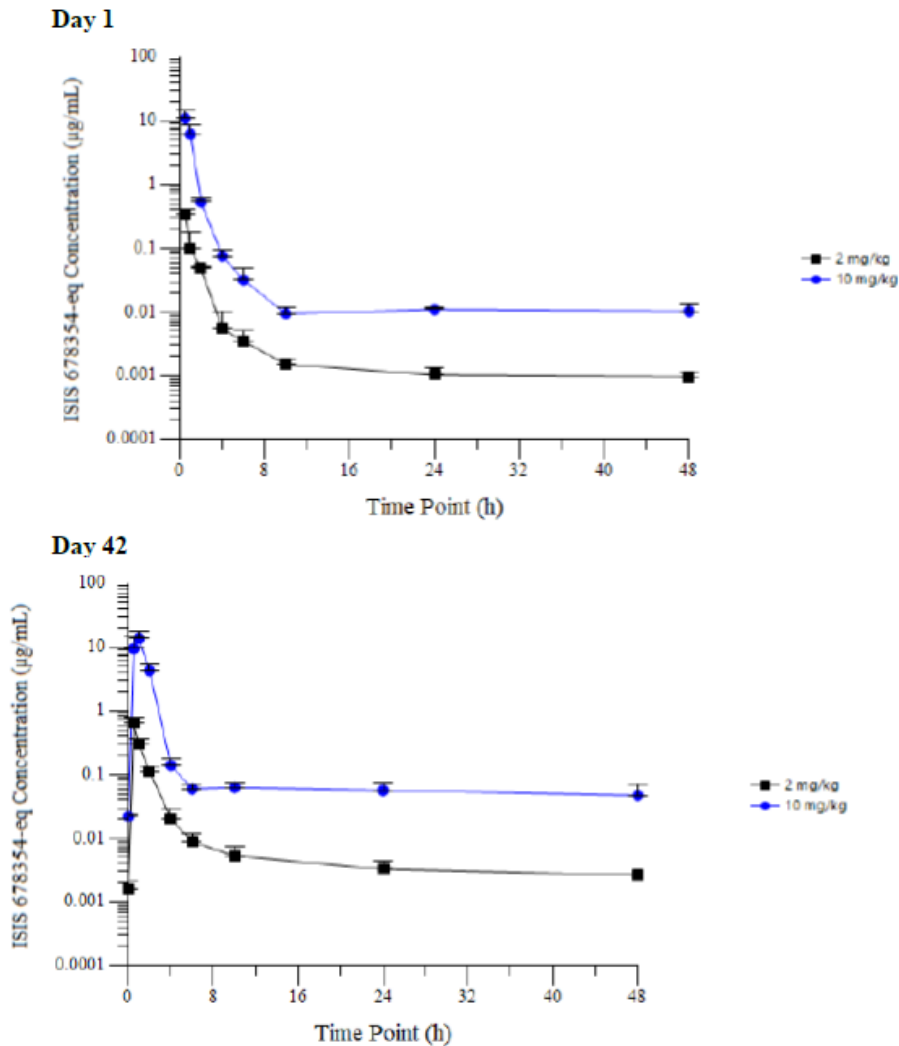
Olezarsen was quantified in plasma using quantitative hybridization assay coupled with electrochemiluminescence (ECL) and in tissues using high-performance liquid chromatography with tandem mass spectrometry. In addition, liver and kidney concentrations were measured in the chronic mouse and monkey studies and in F₀ mice as part of the fertility and early embryonic development study.

Absorption

Across nonclinical species, the PK profiles were qualitatively comparable. Olezarsen rapidly enters plasma following SC administration and is then quickly distributed into tissues where it is metabolized by nucleases releasing the active ASO.

In mice, olezarsen was rapidly absorbed (time to maximum concentration [T_{max}] = 0.5 to 1 hour). After reaching peak levels, plasma concentrations declined rapidly over the first 8 to 12 hours. Clearance was multi-phasic with an initial quick decline from plasma followed by a more prolonged decline from tissues. The mean residence time ranged from 2 to 5 hours at the doses evaluated and was similar between doses at each time point. Mean peak concentration (C_{max}) and total plasma exposure (AUC_{0-48h}) increase with dose in a greater than proportional manner. Plasma drug levels following repeated dosing were higher than after the initial dose administration suggesting accumulation. There were no sex differences in exposure. Exposure profile curves are shown in [Figure 42](#).

Figure 42. Exposure Profile Curve of ISIS 678354 in Mice



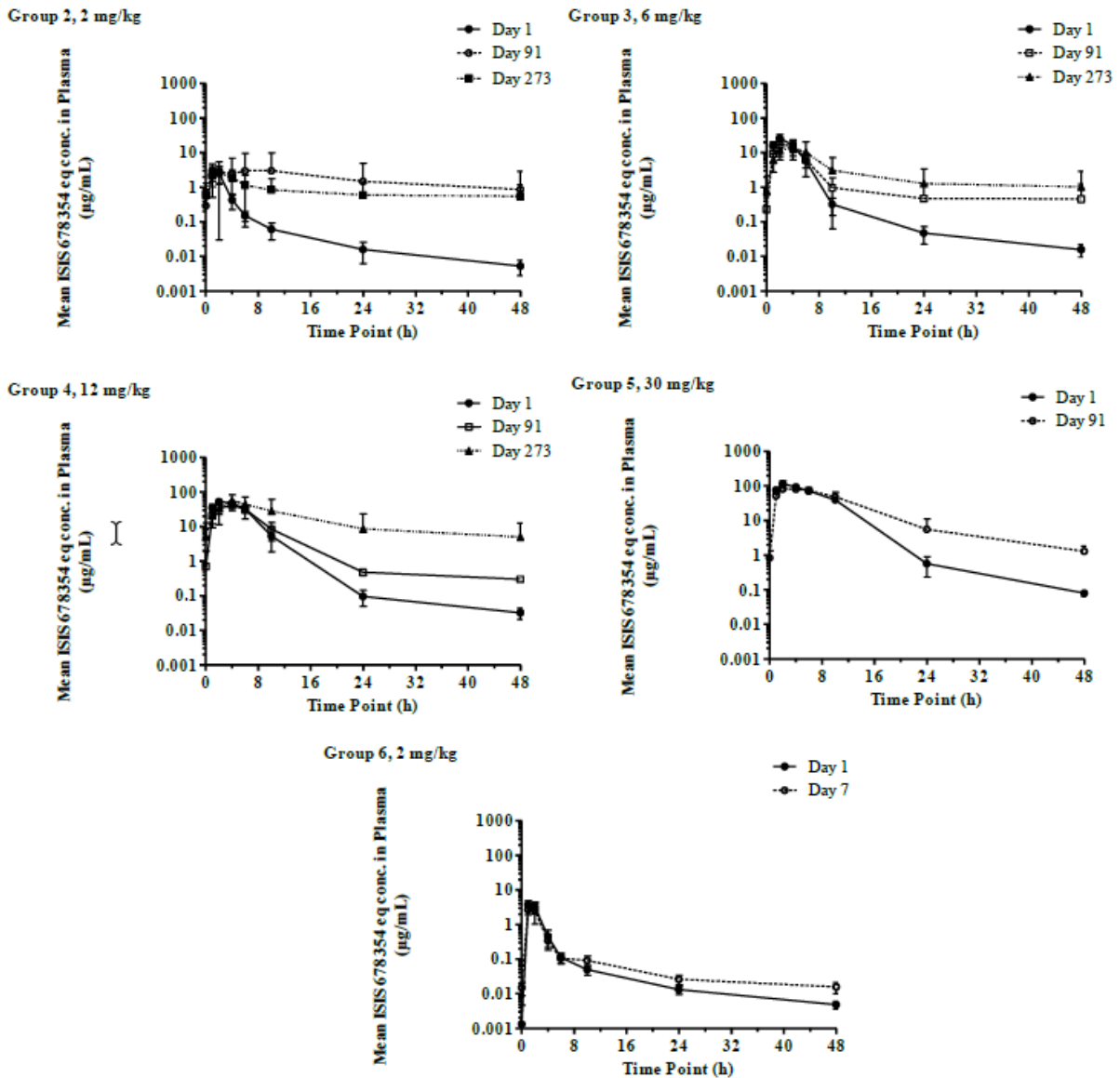
Data presented are mean + standard deviation (N = 3)

Source: Study No. 678354-APK01PK, Figure 1

Source: Figure 1 of Applicant's Pharmacokinetic Written Summary, modified by reviewer to remove Applicant's figure title

In the monkey, rapid absorption was also seen ($T_{max} = 1$ to 4 hours), followed by a more prolonged clearance phase, with a half-life of approximately 30 days following repeated administration. C_{max} and AUC_{0-48h} increased greater than dose proportionally over the dose ranges evaluated, with levels generally 2- to 4-fold higher in antidrug antibody (ADA)-positive animals. In ADA-positive animals, plasma trough levels were also higher than in ADA-negative animals. There was no apparent accumulation in ADA-negative animals, but there was in ADA-positive animals, likely resulting from olezarsen binding to ADA in plasma. No sex differences in exposure were identified. Exposure profiles are shown in [Figure 43](#) below.

Figure 43. Exposure Profile Curve of ISIS 678354 in Monkeys



Symbols represent the group mean and error bars represent standard deviation (N = 5 to 14)

Source: Study No. 678354-AS02PK, Figure 2

Source: Figure 2 of Applicant's Pharmacokinetic Written Summary, modified by reviewer to remove Applicant's figure title
Abbreviations: conc., concentration

Pharmacokinetics in monkeys is considered predictive of human PK for this class of compound. The PK profiles from monkeys and humans are summarized in [Table 92](#) below.

Table 92. Comparison of ISIS 678354 Plasma PK Parameters Between Monkey and Human

Species	Study Number	Dose Level (mg/kg)	N	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-48h} (µg [*] h/mL)	CL/F ^a (mL/h/kg)	t _{1/2} ^b (day)
Monkey	AS02	2 ^c	14	4.01 ± 1.16	2 (1, 2)	9.53 ± 2.44	224 ± 60.8	24.4 ^d
		2	14	3.28 ± 1.71	1 (1, 2)	8.35 ± 3.11	270 ± 92.1	NA
		12	18	54.5 ± 11.1	2 (2, 4)	322 ± 57.4	38.5 ± 7.19	29.7 ± 8.67 ^e
Human	CS1	0.86 ^f	6	0.284 (24.4)	1 (1, 4)	2.78 (16.5)	219 (13.0)	18.9 (36.0)
		1.3 ^f	6	1.06 (81.0)	1.25 (1, 4)	6.71 (30.9)	157 (29.5)	39.7 (88.8) ^g

Note: Values are presented as mean ± SD [animals] or geometric mean (geometric mean coefficient of variation) [human], except T_{max}, which is presented as median (min, max). SD not present when N ≤ 2. Olezarsen concentration measured as total full-length ASO, which includes fully conjugated, partially conjugated (olezarsen with 1, 2, or 3 GalNAc sugar deletions), and unconjugated olezarsen.

^a CL/F was calculated by actual dose/AUC, where AUC was AUC_{0-48h} in animals and AUC_{last} in humans

^b t_{1/2} in animals were determined after repeat dose administration

^c Data from Group 6 (PK) animals

^d t_{1/2} for Group 6 on Day 7 was calculated using sparse sampling function in Phoenix WinNonlin

^e N = 4

^f Body weight normalized doses (mg/kg) were estimated based on fixed doses of 60 and 90 mg divided by 70 kg (assumed human body weight)

^g N = 5

ASO = antisense oligonucleotide; AUC = area under the curve; C_{max} = maximum observed concentration;

NA = not applicable; SD = standard deviation; t_{1/2} = terminal elimination half-life

Source: Study No. 678354-AS02PK, Table 13 and ISIS 678354-CS1, Table 22

Source: Table 6 of Sponsor's pharmacokinetic written summary, modified by reviewer to remove Applicant's table title. Abbreviations: CL/F, apparent clearance; PK, pharmacokinetics; T_{max}, time to maximum plasma concentration

Distribution

The distribution of olezarsen was evaluated in mice and monkeys. Olezarsen is highly bound to plasma proteins (>98%) in the mouse and monkey and was similar to that in human plasma. The mean blood to plasma ratios in human and monkey ranged from 0.488 to 0.98 at concentrations up to 300 µg/mL, whereas in mouse, mean blood to plasma ratios was ~1. Distribution to tissues in mouse and monkey was responsible for the initial rapid plasma clearance, with the highest concentrations present in liver and kidney. In both species, concentrations in the liver were higher compared to kidney cortex at the lower doses evaluated, most likely attributed to more efficient uptake of GalNAcs by the asyloglycoprotein receptor in the liver. The concentration in the kidney cortex increased approximately dose-proportionally, whereas in the liver, it increased less than dose-proportionally, likely due to saturation of asyloglycoprotein receptor-mediated hepatocyte uptake at the higher doses evaluated in both species (12 and 20 mg/kg/wk in mouse and monkey, respectively) which limited further uptake into the liver. The saturation occurred at high multiples of the proposed clinical dose (80 mg/month, or 0.285 mg/kg/wk). Near steady-state tissue exposure levels were achieved after 13 weeks of once-weekly dosing in both mouse and monkey. Minimal levels were reported in both tissues following recovery periods, consistent with terminal tissue half-lives of approximately 4 weeks in both species. Data are summarized in [Table 93](#) (mice) and [Table 94](#) (monkey) below.

Table 93. Tissue Concentrations of Unconjugated ISIS 678354 in Mice Following 26 Weeks of Treatment

Group	Dose Level (mg/kg/wk)	Day of Collection	Time After Last Dose (days)	N	Unconjugated Olezarsen (µg/g)	
					Kidney	Liver
2	2	184	2	12	6.01 ± 1.05	17.5 ± 2.25
3	6	184	2	12	41.8 ± 13.3	55.0 ± 16.8
4	20	184	2	12	173 ± 91.9	165 ± 30.9
		273	91	12	0.985 ± 1.01	1.73 ± 1.98

Note: Values are presented as mean ± standard deviation

Source: Study No. 678354-AS04PK, Table 1

Source: Table 8 of Applicant's pharmacokinetic written summary, modified by reviewer to remove Applicant's table title

Table 94. Tissue Concentrations of Unconjugated ISIS 678354 in Monkeys Following 39 Weeks of Treatment

Group	Dose Level (mg/kg/wk)	Day of Collection	Time After Last Dose (days)	N	Unconjugated Olezarsen (µg/g)	
					Kidney Cortex	Liver
2	2	93	2	6	152 ± 87.1	274 ± 88.9
		275	2	8	126 ± 27.6	400 ± 97.8
3	6	93	2	6	420 ± 124	622 ± 108
		275	2	8	360 ± 104	759 ± 176
4	12	93	2	6	1108 ± 398	1105 ± 207
		275	2	8	809 ± 185	971 ± 274
		455	182	4	13.0 ± 16.3	13.7 ± 12.6
5	30	93	2	6	2934 ± 1564	1460 ± 318
		275	184	4	51.2 ± 40.6	3.70 ± 1.69

Note: Values are presented as mean ± standard deviation

Source: Study No. 678354-AS02PK, Table 4

Source: Table 9 of Applicant's pharmacokinetic written summary, modified by reviewer to remove Applicant's table title

In monkeys, there were no notable differences in tissue concentrations between ADA-positive and ADA-negative animals.

Metabolism

Across species, the metabolism of olezarsen begins with an initial hydrolysis of the GalNAc3 to form the unconjugated ASO in tissues. The unconjugated ASO is metabolized in tissues by intracellular nucleases to produce chain-shortened oligonucleotide metabolites, consistent with endonuclease cleavage followed by sequential exonuclease cleavage of deoxyphosphorothioate linkages.

In mouse and monkey plasma, fully conjugated olezarsen was the major circulating species within the first 24 hours postdose, accounting for 69% to 93% of the detected analytes. N-1 to N-15 chain-shortened metabolites and unconjugated drug accounted for the remaining analytes.

NDA 218614

Tryngolza (olezarsen sodium)

Prior to subsequent dosing, unconjugated drug accounted for the nearly total abundance of analyte detected.

In the liver and kidney of mouse and monkey, full-length oligonucleotide primarily associated with unconjugated olezarsen was the most abundant species (>80%), with multiple chain shortened oligonucleotide metabolites (N1-N15) accounting for anywhere from <1% to <7% of the total peak area in mice, and <1% to <2% in monkeys. In urine, unconjugated drug was the major component.

Eight linker-related metabolites (M5-M12) were detected in mouse plasma and 10 metabolites (M4-M12 and M14) in monkey plasma, with highest levels typically seen 2 hours after dosing. Concentrations were <6% of parent levels. Levels were decreased up to 10-fold further by 24 hours and were inconsistently able to be detected prior to subsequent dose administration. In mouse urine, linker metabolites were predominantly excreted in the first 24 hours.

Human plasma was collected and analyzed for fully conjugated drug and metabolites at pre-dose and/or 2 hours postdose at various study days in clinical Trial ISIS 678354-CS1 and reported in study 678354-IS13. Full length drug was the only analyte detected, accounting for 100% of the peak area in all samples. In human urine collected in clinical Trial ISIS 678354-CS1 and reported in study 678354-IS0999, unconjugated olezarsen (i.e., volanesorsen) is the most abundant component, while various chain-shortened metabolites accounted for the remainder. Overall, the metabolite profile in plasma and urine was similar between nonclinical species (mouse and monkeys) and humans and there were no unique metabolites identified in humans compared to animal species.

Excretion

Excretion of the unconjugated olezarsen and its metabolites occur predominantly through urine, and to a lesser extent through feces.

In mouse urine, full-length olezarsen represented <1% of the administered dose during the initial 48 hours following administration; the major component was unconjugated olezarsen. In human urine, unchanged fully conjugated olezarsen was the major oligonucleotide component, with several oligonucleotide metabolites associated with olezarsen 3'-deletion that still retained some of the linker component attached, as well as chain-shortened oligonucleotides from unconjugated olezarsen were detected.

Anti-Drug Antibodies

ADA levels were measured in the chronic monkey study. ADA were detected in animals from all treated groups (30-64%) and controls (22%). The plasma trough levels of olezarsen were increased approximately up to 6-fold in ADA+ animals as compared to that reported in ADA- animals following 3 months or more treatment, suggesting olezarsen binding to ADA in plasma. However, there were no notable differences in tissue levels of drug between ADA+ and ADA- animals. Furthermore, the presence of ADAs had no significant effects on the toxicity profile or pharmacologic endpoints (hepatic *apoC-III* mRNA levels).

Toxicokinetics

Toxicokinetic data and/or tissue drug levels were collected as a component of various repeat-dose toxicity studies. Descriptions of pertinent TK data are summarized with the results of individual toxicology studies (refer to Section [13.3.3](#)).

13.3.3. Toxicology

The toxicology of olezarsen has been characterized in repeat-dose toxicity studies, a fertility and early embryonic developmental study, a battery of in vitro and in vivo genotoxicity studies, and an impurity qualification study. The toxicity of the active, unconjugated ASO (volanesorsen) on embryo-fetal development, pre-postnatal development, and its carcinogenic potential were previously assessed in support of the marketing application for that product. In agreement with the Agency, these studies with the unconjugated ASO were considered supportive of the current application.

General Toxicology

The general toxicity of olezarsen has been characterized in repeat-dose toxicity studies in CD-1 mice and cynomolgus monkeys in studies of up to 26- and 39-weeks duration, respectively, with once-weekly SC injections. These studies included 13- and 26-week recovery periods in the mouse and monkey, respectively. The no observed adverse effect levels (NOAELs), basis for the NOAELs, and the safety margins based on body surface area (BSA) are captured in [Table 95](#) below. The summary table is followed by more detailed reviews of the pivotal toxicology studies conducted with olezarsen that support this application.

Drug-related effects consistent with the expected toxicities of an ASO with a phosphorothioate backbone were evident in the liver, kidney, and spleen. Tissue effects at the injection site were also observed. The most notable effect was thrombocytopenia, observed in both the mouse and NHP.

Table 95. Safety Margins From Pivotal Repeat-Dose Toxicity Studies With Olezarsen Based on Body Surface Area

Study (Doses)	NOAEL (mg/kg/wk)	BSA (mg/m²)	Margins to NOAEL/LOAEL^a (multiples based on BSA)	Basis for NOAEL
26-week mouse (0, 2, 6, 20 mg/kg/wk; the mouse specific ASO ISIS 838707 was also evaluated at 6 mg/kg/wk)	2	6	0.5x/1.5x	- Increased AST, ALT, ALP (up to ~3- ~7- and ~2-fold, respectively) at 20 mg/kg/wk (~5x MRHD_{BSA}). - Dose-related increased (~2-fold) absolute and relative weights of liver and spleen at ≥ 6 mg/kg/wk (~1.5x MRHD_{BSA}). - Increased incidence/severity of hepatocellular hypertrophy, cytoplasmic alteration, karyomegaly, increased mitotic figures and vacuolated/granular macrophages in the liver at ≥ 6 mg/kg/wk - Increased incidence/severity of red pulp cellularity in the spleen at ≥ 6 mg/kg/wk
39-week monkey (0, 2, 6, 12, 30 mg/kg/wk)	6	72	6x/12x	Significant decrease (>98%) in platelet count in one male monkey at 12 mg/kg/wk.

Source: Reviewer-generated table.

^a Human dose = 80 mg/month, equivalent to 1.33 mg/kg/month for a 60-kg adult. This is equivalent to 49 mg/m² based on BSA. Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; ASO, antisense oligonucleotide; AST, aspartate aminotransferase; BSA, body surface area; LOAEL, lowest observable adverse effect level; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; wk, week(s)

Individual Study Summaries

26-Week Repeat Dose Toxicity Study of ISIS 678354 in Mice With a 13-Week Recovery Period (Study No. 678354- AS04)

Dosages of 2, 6, or 20 mg/kg were administered once weekly by SC injection for 26 weeks followed by a 13-week recovery period (control and 20 mg/kg). An additional group was also administered a murine specific version of the same ASO (ISIS 838707) at 6 mg/kg/wk to evaluate target-related toxicity.

Key Study Findings

- Increases in aspartate aminotransferase (AST) (up to ~ 3-fold), alanine aminotransferase (ALT) (up to ~7x) at 20 mg/kg/wk dose in both sexes compared to controls. These effects were reversible.
- Increase in alkaline phosphatase (up to ~2-fold compared to control) in males at 20 mg/kg/wk that resolved during recovery.
- Reversible increase in monocyte chemoattractant protein-1 (MCP-1) (~8-fold compared to control) in both sexes at 20 mg/kg/wk, which suggests an inflammatory response because MCP-1 is a potent inflammatory cytokine.
- Immunoglobulin M (IgM) decreased in males at ≥ 6 mg/kg/wk (up to 40% lower) and in females at ≥ 2 mg/kg/wk (up to 58%).
- Dose-related increased absolute and relative weights for liver (1.2 to 1.6-fold) and spleen (1.6 to 1.9-fold over control) at ≥ 6 mg/kg/wk in both sexes compared to controls, which correlated with microscopic findings in the liver (hepatocellular hypertrophy, cytoplasmic alteration, karyomegaly, increased mitotic figures and vacuolated/granular macrophages) and spleen (red pulp cellularity), respectively.
- Decreased absolute and relative thymus weights (-41% to -45% lower) at 20 mg/kg/wk in both sexes, which correlated with increased generalized lymphoid depletion in all animals administered 20 mg/kg/wk.
- The absolute and relative liver weight increase (1.1 to 1.2-fold); spleen weight increase (1.4 to 1.5-fold) and thymus weight decrease (-30 to -59%) and microscopic findings persisted at 20 mg/kg/wk during recovery.
- Increased absolute and relative kidney weight (~1.2-fold), cytoplasmic basophilic granules in the tubular epithelial cells and minimal tubular vacuolation.
- Decreases in hepatic *apoC-III* mRNA expression (~ -88%), plasma TG (~ -49% lower, relative to control), and mild increases in MCP-1 (~2-fold over control) with the ISIS 838707 (the mouse specific inhibitor).
- Tissue concentration ($\mu\text{g/g}$) of unconjugated olezarsen following multiple SC administration (48 hours after last dose) with recovery demonstrated dose-dependent increases in the liver and kidney, with more than dose-proportional increase in the kidney, and low concentrations in reproductive organs compared to kidney and liver in CD-1 mice.

The no observed adverse effect level (NOAEL) for the 26-week mouse study was 2 mg/kg/wk, based on the dose-related pattern, incidence, and severity of the microscopic findings in the liver and spleen, which correlated with increased absolute and relative organ weights at ≥ 6 mg/kg/wk and minimal to marked increases in liver enzymes, resulting in a 0.5x safety margin based on BSA at the maximum recommended human dose of 80 mg/month. The pharmtox reviewer's identified NOAEL differs from that determined by the Applicant. The Applicant considered only liver, spleen, and thymus effects (organ weight changes and microscopic findings) at 20 mg/kg/wk to be adverse because they persisted through recovery and identified 6 mg/kg/wk as the NOAEL.

Study Information

Table 96. Study Information

Study Features and Methods	Description
GLP compliance:	Yes
Doses and frequency of dosing:	0, 2, 6, 20 mg/kg/week for 26 weeks
Route of administration:	Subcutaneous
Formulation/vehicle:	10 mL/kg / 0.9% NaCl
Species/strain:	CD-1 (ICR)
Number/sex/group:	12 (LD and MD) / 18 (C and HD)
Age:	6 weeks at receipt
Satellite groups/unique design:	6 (C recovery and HD recovery) 6 (treated with a murine apoC-III inhibitor [ISIS 838707] at MD)

Source: Reviewer-generated table.

Abbreviations: C, control; GLP, Good Laboratory Practice; HD, high dose; LD, low dose; MD, mid dose

Dose Justification

The dosages used in the 26-week study were based on results from the 13-week study conducted in CD-1 mice administered 0, 2, 6, or 24 mg/kg once weekly by SC administration. The key finding from this study pertinent to dosage selection was a 25% reduction in platelet count (thrombocytopenia) in all 24 mg/kg/wk females which was reversible. Thrombocytopenia was also seen with the unconjugated ASO (volanesorsen).

Observations and Results

The primary observations from the 26-week mouse study and tissue concentrations of the drug are summarized in [Table 97](#) and [Table 98](#).

Table 97. Summary of Results From 26-Week Mouse Study

Endpoints	Major Findings
Endpoints with notable observations	
Food consumption (FC)	Slightly higher FC (0.5g to 1.2 g/week) in 20 mg/kg/wk males compared to control during multiple weeks of treatment.
Clinical chemistry	Increases in ALT (up to ~7-fold), AST (up to ~3-fold) at 20 mg/kg/wk in both sexes compared to control. Increases in ALP (up to ~2-fold) in 20 mg/kg/wk males compared to controls. Decrease in albumin (-7%) and increase in MCP-1 (up to ~8-fold compared to control) in both sexes at 20 mg/kg/wk. These effects were treatment-related because they correlated with microscopic liver findings but resolved in the recovery group. IgM decreased in males at ≥ 6 mg/kg/wk (up to 40% lower) and in females at $\geq$ LD (up to 58%). Effect was reversible in recovery group. IgG level was increased (~32%) at 2 mg/kg/wk females compared to controls with no dose response.
Hematology	Red cell mass decrease (erythrocytes, hemoglobin, hematocrit; up to ~14% lower) at 20 mg/kg/wk in both sexes compared to mean control. Resolved during recovery period. There were no effects on platelet counts.

Endpoints	Major Findings
Organ weight	Dose-related increased absolute and relative weights for liver (1.1- to 1.6-fold); spleen (1.3- to 1.9-fold) at ≥ 6 mg/kg/wk in both sexes compared to controls; decreased thymus weight (-41% to -45%) at 20 mg/kg/wk in both sexes; increase absolute and relative kidney weight in 20 mg/kg/wk males (~1.2-fold).
Histopathology	Dose-related increased incidence and/or severity in: Liver (hepatocellular hypertrophy, cytoplasmic alteration, karyomegaly, increased mitotic figures and vacuolated/granular macrophages) ≥ 6 mg/kg/wk. Spleen (increased red pulp cellularity) at ≥ 6 mg/kg/wk in both sexes. Thymus (increased generalized lymphoid depletion) at 20 mg/kg/wk in both sexes. Kidney (cytoplasmic basophilic granules in the tubular epithelial cells and minimal tubular vacuolation).
Injection site reaction	Microscopic observations were noted at 6 and/or 20 mg/kg/wk at the injection site (vacuolated/granular macrophages, mononuclear cell and/or mixed leukocyte infiltration)
Endpoints without notable observations	No drug-related adverse effects on mortality, clinical signs, body weight, ophthalmologic endpoints, and macroscopic observations.
Observations with ISIS 838707	Significant decrease in hepatic apoC-III mRNA (~88%), decreases in triglyceride (~ -49% lower, relative to control) and mild increases in MCP-1 (~2-fold over control); vacuolated / granular macrophages at injection sites.

Source: Reviewer-generated table.

Abbreviations: ALT, alanine aminotransferase; ; AST, aspartate aminotransferase; FC, food consumption; Ig, immunoglobulin; LD, low dose; MCP-1, monocyte chemoattractant protein-1; wk, week(s)

Table 98. Tissue Concentration ($\mu\text{g/g}$) of Unconjugated ISIS 678354 Following Multiple SC Administration (48 Hours After Last Dose) With Recovery in CD-1 Mice

Study Day	Dose (mg/kg/wk)	Kidney	Liver	Testes	Ovaries	Uterus
Day 184	2	6	17.5	NA	NA	NA
(Terminal)	6	41	55.0	NA	NA	NA
	20	173	165	13.7	30.0	19.1

Source: Compiled by PharmTox Reviewer using Data from Tables R and S of study report 678354-AS04

Abbreviations: NA, not applicable; SC, subcutaneous; wk, week(s)

39-Week Repeat Dose Toxicity Study of ISIS 678354 in Monkey With a 13-Week Interim Necropsy and a 26-Week Recovery Period (Study No. 678354- AS02)

SC dosages of 2, 6, and 12 mg/kg were administered for 39 weeks followed by a 26-week recovery period at 12 mg/kg. These groups also included animals terminated at 13 weeks. Additionally, a dosage of 30 mg/kg was administered for 13 weeks; this group also included a 26-week recovery period.

Key Study Findings

- A single male administered 12 mg/kg/wk had very low platelet counts on both Day 65 and at the interim termination at Week 13.
- Increases in glutamate dehydrogenase (up to 5-fold baseline), ALT (4-fold baseline), AST (1.6x baseline) were evident at ≥ 6 mg/kg/wk. Decreases in albumin (~13-30% lower) in both

sexes at ≥ 6 mg/kg/wk and A:G ratio (~40% lower), and creatinine were also seen, primarily at dosages ≥ 12 mg/kg/wk. Liver enzyme increases correlated with microscopic findings in the liver. These effects on serum chemistry parameters were reversible in the recovery group.

- At dosages ≥ 12 mg/kg, basophilic granules were found in the liver (in hepatocytes and Kupffer cells; associated with Kupffer cell hypertrophy), kidney, lymph nodes, and multiple other tissues. Additional findings were noted in the liver (glycogen vacuolation), kidney (tubular cell vacuolation), and injection site (mononuclear cell infiltration) was observed at the injection site. There were no microscopic correlates to the heavier spleen. Basophilic granules were still present in multiple tissues following recovery.
- Dose-related reduction in hepatic *apoC-III* mRNA levels and plasma protein levels and plasma TG levels were evident. Both showed reversal following the recovery period.
- Plasma exposure increased with dose in a greater than proportional manner, there were no sex differences, and there was minimal accumulation. A similar pattern was seen in liver and kidney tissues. The half-life in both plasma and tissues ranged from 20 to 30 days.
- ADA-positive animals were identified in all groups. The overall incidence of animals testing positive for ADA's ranged from approximately 30% to 64% in those administered olezarsen for 39 weeks while the incidence in controls was 22%. Following recovery, 50% of animals administered 12 mg/kg/wk and 75% of those administered 30 mg/kg/wk remained ADA-positive.
- Olezarsen was rapidly absorbed from plasma with T_{max} occurring by 4 hours after dose administration, exposure increased with dose in a greater than proportional manner. The non-linearity was attributed to higher clearance at the lower dose levels as compared to that at the higher dosages administered. There was no sex difference in exposure and minimal accumulation.
- The plasma terminal elimination half-life ($t_{1/2}$) was estimated to be approximately 30 days based on data generated at 12 and 30 mg/kg/wk supporting the once-monthly dosing regimen.
- Following absorption from plasma, rapid distribution to tissues (liver and kidney), with less than 2-fold difference in levels between the tissues (liver had more than kidney).
- The calculated $t_{1/2}$ following 13 and 39 weeks of treatment in kidney tissue was approximately 30 days and in liver was 21 to 29 days.
- Hepatic *apoC-III* mRNA and ApoC-III protein expression in plasma were reduced in a dose-dependent manner, up to 90% after up to 39 weeks of treatment at doses ≥ 2 mg/kg/wk.

The NOAEL was identified as 6 mg/kg/wk, based on the thrombocytopenia observed in a single animal at 12 mg/kg/wk and the increased incidence/severity of microscopic alterations in liver and kidney that were not completely resolved following the recovery period at dosages ≥ 12 mg/kg/wk. This NOAEL of 6 mg/kg/wk gives a 6x safety margin based on BSA relative to maximum recommended human dose of 80 mg/month. The lowest observable effect level of 12 mg/kg/wk at which thrombocytopenia was observed gives a 12x safety margin.

Additional Comments

Thrombocytopenia was a drug-related effect seen with olezarsen in a single male administered 12 mg/kg/wk on Days 65 and Day 93. In comparison, thrombocytopenia occurred in multiple animals at comparable mg/kg dosage levels that correlated with clinical signs of severe bruising and petechia leading to early terminations and/or dosing holidays in studies with the active unconjugated ASO volanesorsen.

Table 99. Study Information, 39-Week Monkey Study

Study Features and Methods	Description
GLP compliance:	Yes
Doses and frequency of dosing:	0, 2, 6, 12 and 30 mg/kg/wk for 39 weeks (30 mg/kg/wk administered for 13 weeks followed by recovery period).
Route of administration:	Subcutaneous
Formulation/vehicle:	10, 30, 60 and 150 mg/mL / 0.9% NaCl
Species/strain:	Cynomolgus monkey
Dose/number/sex:	0, 2, 6 and 12 mg/kg/wk (n=7, with 3 terminated at interim and 4 at terminal) Recovery groups (n=9) as follows: Control (n=2) following 39 weeks of treatment; at 12 mg/kg/wk, there were 3 recovery animals at end of interim treatment and 4 recovery animals following 39 weeks of treatment. 30 mg/kg/wk (n=5, with 3 terminated at interim and 2 after a 26-week recovery period).
Age:	2-5 years
Satellite groups/unique design:	13-week interim termination (Day 93); 39-week terminations (Day 275); 26-week recovery groups following both 13 and 39 weeks of treatment.
Satellite groups/unique design:	An additional group (n=7) administered 2 mg/kg/wk was used for PK analysis.

Source: Reviewer generated table

Abbreviations: GLP, Good Laboratory Practice; PK, pharmacokinetics; wk, week(s)

Observations and Results

Observations from the 39-week monkey study and plasma and tissue concentrations of the drug are summarized in [Table 100](#), [Table 101](#), and [Table 102](#).

Table 100. Summary of Results, 39-Week Monkey Study

Endpoints	Major Findings
Endpoints with notable observations	
Clinical chemistry	Increases in glutamate dehydrogenase (GLDH) (up to 5-fold baseline), ALT (4-fold baseline), AST (1.6x baseline) were evident at ≥ 6 mg/kg/wk. Decreases in ALB (~13-30% lower) in both sexes at ≥ 6 mg/kg/wk and A:G ratio (~40% lower), and CREA were also seen, primarily at dosages ≥ 12 mg/kg/wk. Liver enzyme increases correlated with microscopic findings in the liver. These effects on serum chemistry parameters were reversible in the recovery group. IgM was slightly increased (1.6-1.7-fold over baseline) in both sexes at ≥ 12 mg/kg/wk during interim sacrifice. Slight increase in IgG in one male at 2 mg/kg/wk and 2 females in 30 mg/kg/wk group. Dose-dependent increases in complement Bb were seen at all dosages at one or more timepoints. Up to 3-fold (females) and up to 21-fold (males) at 12 and 30 mg/kg/wk and up to 3.6-fold (males) and 5.5-fold (females) at ≥ 2 mg/kg/wk. Increases in complement Bb was accompanied by decreases in complement C3 was seen at all dosages in males and at 12 and 30 mg/kg/wk in females. Effects indicative of generalized inflammation included increases in CRP, MCP-1, and/or IFNγ levels, primarily at dosages > 12 mg/kg. These effects on serum chemistry parameters were reversible in the recovery group.
Hematology	A single male administered 12 mg/kg had low platelet counts ($>98\%$ decrease) during the 13-week treatment interval but survived to scheduled interim termination. Transient prolongation of activated partial thromboplastin time (APTT) times (up to 1.5x baseline) occurred at 30 mg/kg/wk.
Organ weight	The liver, lymph nodes, and spleen were grossly enlarged and / or had increased weights. At terminal sacrifice, absolute liver weight increased in males at ≥ 6 mg/kg/wk (≥ 1.5-fold); absolute and relative liver weight increased in females at ≥ 12 mg/kg/wk (~1.7-fold and ~1.5-fold, respectively). Spleen weight in females at 12 mg/kg/wk increased by ~2-fold. Effects on organ weights were reversible.
Histopathology	At dosages ≥ 12 mg/kg, basophilic granules were found in the liver (in hepatocytes and Kupffer cells; associated with Kupffer cell hypertrophy), kidney, lymph nodes, and multiple other tissues. Additional findings were noted in the liver (glycogen vacuolation), kidney (tubular cell vacuolation), and injection site (mononuclear cell infiltration). There were no microscopic correlates to the heavier spleen. Basophilic granules were still present in multiple tissues following recovery
Anti-Drug Antibodies (ADAs) / Immunogenicity	The presence of ADA had no effect on exposures on days 1 and 91; at day 273, exposures were 2 to 4-fold higher in ADA positive animals. There were no differences in hepatic apoC-mRNA, C3 and platelet count between ADA positive and ADA negative animals after 9 months of treatment. There was no effect on the ability of the animals to mount an immune response based on T-cell dependent antibody responses (TDAR) to KLH challenges.
Endpoints without notable observations	No drug-related adverse effects on survival, clinical observations, body weights, food consumption, ophthalmoscopic examinations, ECGs, blood pressure, urine analysis, urine chemistry or cytokine/chemokine.

Source: Reviewer generated table

Abbreviations: A:G, albumin:globulin; ADA, antidrug antibody; ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CREA, creatinine; CRP, C-reactive protein; ECG, electrocardiogram; GLDH, glutamate dehydrogenase; IFN, interferon; Ig, immunoglobulin; KLH, keyhole limpet hemocyanin; MCP-1, monocyte chemoattractant protein-1; TDAR, T-cell dependent antibody responses; wk, week(s)

Table 101. Summary of Plasma Toxicokinetic Parameters of Total Full-Length (ISIS 678354-Equivalent) Following Single and Multiple Subcutaneous Administrations of ISIS 678354 in Cynomolgus Monkeys

Group	Dose Level (mg/kg)	Profile Day	N	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-24h} (µg ² h/mL)	AUC _{0-48h} (µg ² h/mL)	CL _{0-48h/F} (mL/h/kg)	MRT _{0-48h} ^a (h)	t _{1/2} ^b (days)
2	2	1	14	3.28 ± 1.71	1 (1, 2)	8.12 ± 3.07	8.35 ± 3.11	270 ± 92.1	4.13 ± 1.10	NA
		91	6	4.54 ± 6.32	2 (1, 10)	56.2 ± 119	83.8 ± 183	208 ± 127	11.9 ± 4.33	NA
		273	8	2.64 ± 1.32	2 (1, 2)	25.0 ± 22.0	38.7 ± 37.9	95.2 ± 56.9	16.4 ± 3.22	NA
3	6	1	14	25.8 ± 8.29	2 (1, 2)	99.9 ± 31.0	101 ± 31.0	66.4 ± 25.6	3.66 ± 0.433	NA
		91	6	17.9 ± 8.02	2 (1, 4)	90.7 ± 26.2	102 ± 30.2	63.1 ± 17.0	7.84 ± 5.56	NA
		273	8	15.8 ± 9.77	4 (2, 6)	114 ± 103	141 ± 149	77.4 ± 46.5	10.2 ± 3.81	NA
4	12	1	18	54.5 ± 11.1	2 (2, 4)	320 ± 57.5	322 ± 57.4	38.5 ± 7.19	4.68 ± 0.623	NA
		91	6	42.0 ± 6.44	4 (2, 6)	296 ± 56.4	305 ± 57.8	40.7 ± 8.52	6.67 ± 0.776	NA
		273	12	58.5 ± 27.4	4 (2, 4)	600 ± 549	760 ± 806	28.3 ± 16.2	11.6 ± 3.59	29.7 ± 8.67
5	30	1	10	118 ± 24.5	2 (2, 4)	857 ± 115	863 ± 116	35.3 ± 4.58	6.07 ± 0.489	NA
		91	10	86.5 ± 14.5	2 (2, 6)	930 ± 238	997 ± 268	31.8 ± 7.24	9.41 ± 1.24	30.5 ± 6.38
6 ^c	2	1	14	4.01 ± 1.16	2 (1, 2)	9.33 ± 2.46	9.53 ± 2.44	224 ± 60.8	3.48 ± 0.574	NA
		7	12	3.26 ± 1.01	1 (1, 2)	7.64 ± 2.30	8.13 ± 2.27	268 ± 91.0	5.79 ± 1.48	24.4

Note: Values are presented as mean ± standard deviation, except T_{max}, which is presented as median (min, max)

NA = Not applicable

^a = MRT_{0-48h} was calculated from plasma concentrations ranging from time 0 to 48 hours

^b = Terminal elimination half-life (t_{1/2}) for Group 6 on Day 7 was calculated by using sparse sampling function in Phoenix[®] WinNonlin[®] ver. 6.3

^c = Animals in Group 6 were dosed by SC administration on Days 1, 3, 5, and 7 only (4 doses total).

Source: Applicant's table 2 of the toxicokinetic report from Applicant study 678354-AS02.

Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; t_{1/2}, terminal elimination half-life; T_{max}, time to maximum concentration

Table 102. Tissue Concentrations (µg/g) of Unconjugated ASO Following 13 or 39 Weeks of Treatment in Cynomolgus Monkeys

Study Day	Dose Level (mg/kg/week)	Kidney	Liver
Day 93 (Interim)	2	152 ± 87.1	274 ± 88.9
	6	420 ± 124	622 ± 108
	12	1108 ± 398	1105 ± 207
	30	2934 ± 1564	1460 ± 318
Day 275 (Terminal)	2	126 ± 27.6	400 ± 97.8
	6	360 ± 104	759 ± 176
	12	809 ± 185	971 ± 274
	30 (Recovery)	51.2 ± 40.6	3.70 ± 1.69
Day 455 (Recovery)	12	13.0 ± 16.3	13.7 ± 12.6

Values are presented as mean ± standard deviation (N = 2-8/sex, both sexes combined for analysis)

Source: From Applicant's table 8 of toxicology written summary modified by reviewer to change title

Abbreviation: ASO, antisense oligonucleotide

Genetic Toxicology

Olezarsen was evaluated for genotoxic potential in a battery of good laboratory practice (GLP)-compliant in vitro (Ames bacterial reverse mutation assay and chromosomal aberration assay in Chinese hamster lung cells) and in vivo (mouse bone marrow micronucleus assay) studies, with and without metabolic activation (in vitro), using appropriate positive and vehicle controls. Studies were considered valid as expected results were seen with the positive controls. Olezarsen

was non-genotoxic up to a top dose of 5000 µg/mL in the Ames assay, up to a top dose of 500 µg/mL in the in vitro chromosomal aberration assay in Chinese hamster lung cells, and up to 2000 mg/kg in male CD-1 mice.

Table 103. Summary of Genetic Toxicology Studies

Study No./ Study Title	Key Study Findings
Study No. 678354-IS01/ In Vitro Reverse Mutation Assay in Bacterial cells	Olezarsen was not mutagenic in a standard and valid GLP-compliant Ames assay up to top dose of 5000 ug/ml per plate with and without metabolic activation in any of the tester strains.
Study No. 678354-IS02/ Assay for Chromosomal Aberrations In Vitro in Chinese Hamster Lung (CHL) Cells	Olezarsen tested negative in a standard and valid GLP-compliant in vitro chromosomal aberration assay in CHL cells up to 500 ug/ml in the presence and absence of metabolic activation.
Study No. 678354-AS05/ Assay for Micronucleus Induction in Rat Bone Marrow From a 2-Week Oral Toxicity Study	Olezarsen tested negative in a standard and valid GLP-compliant in vivo micronucleus test in male CD-1 mice up to 2000 mg/kg dosed over 4 days. Liver exposure to olezarsen was confirmed and ranged from 604 to 1407 µg/g.
Other Genetic Toxicology Studies	A dose-ranging finding study was done up to 2000 mg/kg ISIS 678354 dosed over 4 days to determine doses used in the definitive in vivo micronucleus assay above.

Source: Reviewer generated table

Abbreviations: CHL, Chinese hamster lung; GLP, good laboratory practice

Carcinogenicity

Carcinogenicity studies were not conducted for olezarsen. However, carcinogenicity studies were conducted with the active unconjugated ASO volanesorsen.

Two-year carcinogenicity studies were conducted with volanesorsen in CD-1 mice (study no. 304801-AS15) and Sprague-Dawley rats (study no. 304801-AS16) to assess its carcinogenic potential. Results from these studies are summarized below.

In the 2-year mouse study with volanesorsen, dosages of 6, 25, and 40 mg/kg/wk were administered SC. There was reduced survival attributed to cardiomyocyte degeneration associated with inflammatory cell infiltrates at dosages ≥ 25 mg/kg/wk leading to early termination of these groups (Day 625, males at 25 mg/kg/wk; Day 617, females at 25 mg/kg/wk; Day 507, males at 40 mg/kg/wk and Day 487, females 40 mg/kg/wk). Drug-related neoplastic observations were noted at all dosages evaluated. In the liver of male mice, hepatocellular adenomas/carcinomas were increased at dosages ≥ 25 mg/kg/wk, and multicentric hemangiomas/hemangiosarcomas were increased at all doses. In female mice, multicentric histiocytic sarcomas were increased at all doses (including in the group dosed with the mouse-specific oligonucleotide), and pituitary gland adenomas were increased at 25 mg/kg/wk. The liver adenomas, histiocytic sarcomas, and hemangiosarcomas likely reflect the pro-inflammatory properties of the phosphorothioate ASO drug class and the greater sensitivity of rodents to these effects. Pituitary tumors are most likely a reflection of the high background rate of hyperplasia in this species, which is also a relatively common background lesion in aging mice. Thus, although the increased incidences of these tumors are drug-related, the relevance to the clinical population is likely to be limited. As a result of the reduction in survival at the mid dose/high dose (HD),

dose-related increased incidences of cardiovascular effects, and neoplastic effects at all dosages, a NOAEL for the induction of neoplasia was not identified.

In the 2-year rat study with volanesorsen, dosages of 0.2, 1, and 5 mg/kg/wk were administered. Survival was reduced in males at 5 mg/kg/wk due to either masses at injection sites or chronic progressive nephropathy. Drug-related neoplasms observed were increases in the incidences of malignant fibrous histiocytomas (MFH) in the skin/subcutis of the injection sites at dosages ≥ 1 mg/kg/wk in both sexes. The injection site MFH neoplasms with volanesorsen treatment in rats may be attributable to chronic inflammatory reactions associated with repeated SC injections into a limited number of sites and is not likely to be clinically relevant. The NOAEL for the induction of neoplasms in the 2-year rat study is considered the low dose (LD) of 0.2 mg/kg/wk (0.1x the maximum recommended human dose based on BSA comparison of administered dose) based on the increased incidence of MFH at ≥ 1 mg/kg/wk.

In summary, the carcinogenicity studies identified increased incidences of neoplasms in both mice and rats. The majority of these findings were related to the increased sensitivity of these species to the proinflammatory effects of phosphorothioate oligonucleotides and/or the method of administration. As such, the relevance of these findings to the clinical population is limited. Hepatocellular carcinomas, malignant fibrous histiocytomas, hemangiosarcomas, and histiocytic sarcomas have also been reported in carcinogenicity studies with other ASOs. Thus, the presence of these tumors with the unconjugated ASO provides further support that these neoplasms may be a class effect of the phosphorothioate oligonucleotides.

Reproductive Toxicology

A GLP-compliant fertility and early embryonic developmental study was conducted for olezarsen in CD-1 mice (study no. 678354-AS08) because of decreased prostate/seminal vesicle weight and decreased sperm count from the combined fertility and embryo-fetal development mouse study with volanesorsen. Studies evaluating embryofetal development and pre-/postnatal development were not conducted with olezarsen as there were no effects on parameters evaluated in these studies conducted with the unconjugated ASO volanesorsen. The NOAELs from the reproductive toxicology studies conducted with olezarsen and volanesorsen are summarized in [Table 104](#) below.

In [Table 104](#), safety multiples are estimated between the study NOAELs and the clinical dose, based on BSA comparisons. For the estimates, the weekly BSA dose of olezarsen or volanesorsen were multiplied by 2 and 4, respectively, to equate to the once monthly clinical dosing regimen of olezarsen compared to more frequent dosing in animal studies.

Table 104. Summary of Reproductive and Developmental Toxicity Studies

Study/Doses	NOAEL (mg/kg)	NOAEL BSA (mg/m²)	Margins to NOAEL (multiples)	Basis for NOAEL
Study with olezarsen				
FEED CD-1 mice (ISIS 678354)/Study no. 678354-AS08 / 0, 5, 10, 20 mg/kg every other week	20	60	2x ^a	No adverse effect on fertility or embryofetal development at doses evaluated.
Studies with unconjugated active substance volanesorsen (ISIS 304801) and/or ISIS 440670^b				
Combined Fertility/Embryofetal Development of ISIS 304801 and ISIS 440670 ^b in CD-1 mice (Study no. 304801-AS07) / 0, 3, 10, 25 mg/kg every other day; 3 mg/kg of ISIS 440670 every other day	87.5 ^c	262.5	21x ^e	No effect on fertility after 4 weeks of treatment at any dose even though decreased sperm count (↓33%) and decreased prostate/seminal vesicle weight (↓~21%) were evident after 10 weeks of treatment
Combined Fertility/Embryofetal Development of ISIS 440670 ^b in CD-1 mice (Study no. 304801-AS08) / 0, 10, or 25 mg/kg every other day	87.5 ^c	262.5	21x ^d	No adverse effects on fertility endpoints. Slight increases in the incidence of rib ossification variations were noted in drug-treated groups relative to controls that were not statistically different.
EFD rabbit (Study no. 304801-AS09) / 0, 3, 6, or 15 mg/kg every other day	21 ^c	252	20x ^d	Reduced feed consumption, reduced weight gain, and abortion/early delivery at 15 mg/kg every other week.
PPND CD-1 mouse (Study no. 304801-AS17) / 0, 3, 10, or 25 mg/kg every other day	Maternal: 87.5 ^c	262.5	21x ^d	Absence of an effect on reproduction or ability to raise a litter
	F1 Offspring: 35 ^c	105	9x ^d	Reduced weight (up to 15% less than control) at 87.5 mg/kg/wk expressed throughout lifespan

Source: Reviewer-generated table.

a) Human olezarsen dose is 80 mg/month, equivalent to 1.33 mg/kg/month (49.3 mg/m² based on BSA) for a 60-kg adult. Rodent BSA multiplied by 2 to give monthly dose used for calculation of multiple.

b) ISIS 440670 is an antisense inhibitor of mouse *apoC-III* mRNA

c) Every other day dose multiplied by 3.5 to give weekly dose used for determination of BSA dose.

d) The weekly dose BSA was multiplied by 4 to estimate the monthly dose of the unconjugated ASO prior to calculating the margin. This approach was taken based on the active ASO being the same for both drugs.

Abbreviations: ASO, antisense oligonucleotide; BSA, body surface area; EFD, embryofetal development; FEED, fertility and early embryonic development; LOAEL, lowest observable adverse effect level; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

Individual Study Summaries–Reproductive Toxicology Studies With Olezarsen

A Fertility and Embryonic Developmental Study of ISIS 678354 in CD-1 Mice Via Subcutaneous Administration (Study No. 678354-AS08)

Summary: The potential effect of olezarsen on fertility and early embryonic development was evaluated in CD-1 mice. No adverse effects of olezarsen were observed for any parameter, including effects on mating, fertility, and early embryonic development. Consequently, the NOAEL for effects on fertility and early embryonic development was considered the HD of 20 mg/kg.

Key Study Findings

- Slightly increased ALT (~1.7-fold over control) levels in males at 20 mg/kg
- TG levels were reduced to 64% of control levels in HD males and reduced to 59% of controls in females administered doses ≥ 10 mg/kg, consistent with the expected pharmacological effect of the drug.
- Increased absolute and relative liver weights (~1.2 and ~1.1-fold over control) in males at 20 mg/kg, increased absolute and relative spleen weight (~1.2-fold over control) in males at ≥ 10 mg/kg, increased relative kidney weight (~1.1-fold over control) in females at 20 mg/kg.
- Increases (~29% $\uparrow$ over control) in fertility and fecundity indices observed at ≥ 10 mg/kg.

Table 105. Study Information, Mouse FEED Study

Parameter	Method Details
Dose and frequency of dosing:	0, 5, 10 and 20 mg/kg every other week Males: Treatment initiated 10 weeks prior to cohabitation and continued through 14 weeks. Females- Treatment initiated two weeks prior to cohabitation and occurred every other week until evidence of mating. Thereafter, dosages of 0, 0.7, 1.4, and 2.9 mg/kg were administered every other day until implantation on gestation day 6.
Route of administration:	Subcutaneous
Formulation/vehicle:	(b) (4) sodium phosphate /0.9% sodium chloride
Species/strain:	CD-1 Mouse
Number/sex/group:	22
Study design:	Standard design for a FEED study

Source: Reviewer generated table

Abbreviation: FEED, fertility and early embryonic development

Table 106. Observations and Results, Mouse FEED Study

Endpoints	Major Findings
Endpoints with notable observations	
BW and BW gain	Minor (statistically significant) increases in BW and BW gain (~1.1-fold and 1.3-fold, respectively), relative to controls were observed in 20 mg/kg males but not in females.
Clinical chemistry	Slight increase in ALT (~1.7-fold over control) levels in males at 20 mg/kg.
Hematology	Statistically significant slight increase in hemoglobin (3% $\uparrow$ over control) and hematocrit (4% $\uparrow$ over control) in 10 mg/kg males; decrease in microcytosis to 50% of control levels in 10 mg/kg males; increase platelet count (25% $\uparrow$ over control) in females at 5 mg/kg, with no dose response and the magnitude of changes were small.
Organ weights	Increased absolute and relative liver weights (~1.2 and ~1.1-fold over control) in males at 20 mg/kg, increased absolute and relative spleen weight (~1.2 and ~1.2-fold over control) in males at ≥ 10 mg/kg, increased relative kidney weight (~1.1-fold over control) in females at 20 mg/kg.
Fertility and fecundity indices	Statistically significant increases (~29% $\uparrow$ over control) in fertility and fecundity indices at ≥ 10 mg/kg in males and females. These increases were not considered treatment-related because vehicle control groups had relatively low values for fertility and fecundity indices.

Endpoints	Major Findings
Endpoints without notable observations	No drug-related adverse effects on mortality, clinical signs, food consumption, hematology, gross pathology, sperm morphology / sperm count, estrus cycle, precoital time, and fertility parameters.

Source: Reviewer generated table

Abbreviations: ALT, alanine aminotransferase; BW, body weight; FEED, fertility and early embryonic development

Tissue levels of drug in the liver and kidney were measured following termination. Dose-related increases in exposure to olezarsen were noted in both tissues for both sexes. Data are summarized in [Table 107](#) below.

Table 107. Mean Tissue Concentrations of Unconjugated ISIS 678354, Mouse FEED Study

Dose (mg/kg)	Liver (µg/g) ^a		Kidney (µg/g) ^a	
	Maternal	Paternal	Maternal	Paternal
5	4.3 ± 1.12	36.1 ± 5.18	9.3 ± 2.33	13.8 ± 1.68
10	11.4 ± 2.43	55.4 ± 9.12	28 ± 8.41	38.5 ± 17.45
20	26.3 ± 5.49	93.8 ± 10.12	78.9 ± 25.72	67.8 ± 15.57

Data represents Mean ± Standard Deviation (SD)

^a Concentrations are specifically for the unconjugated version of olezarsen

Source: Table 11 of the Applicant's Toxicology Written Summary. Modified by reviewer to revise title.

Abbreviations: FEED, fertility and early embryonic development; SD, standard deviation

Reproductive Toxicology Studies With the Active Unconjugated ASO (Volanesorsen) and/or ISIS 440670

A battery of GLP-compliant reproductive and developmental toxicity studies was conducted to assess the potential effects for the active unconjugated ASO (volanesorsen).

Combination Fertility and Embryofetal Development Study in Mice

In a combined fertility and embryofetal development study in CD-1 mice (study number 304801-AS07), volanesorsen was administered SC at dosages of 3, 10, or 25 mg/kg once every other day (equivalent to 10.5, 35, or 87.5 mg/kg/wk). Males were treated for 4 weeks prior to cohabitation with treated females and continued to be treated for a total of 10 weeks; females were treated for 2 weeks prior to cohabitation and continued treatment until gestational day 15/16. An additional group was administered a murine specific version of this ASO (ISIS 440670) at a dose of 3 mg/kg every other day. In males, treatment with volanesorsen did not result in any adverse effects on fertility following 4 weeks of treatment. However, following 10 weeks of treatment there was a reduction in sperm count (33% lower) and decreased prostate/seminal vesicle weights (↓ ~20%) at 87.5 mg/kg/wk. It is not known if there would have been an effect on fertility endpoints following a longer treatment period. Other effects observed included slight increases in monocytes (up to 4-fold), decreased platelets (reduced up to 32%), and increased ALT (up to 10-fold) and AST (up to 6-fold) in both sexes at 25 mg/kg/wk; the increase in liver enzymes was associated with increased liver weights. Increased spleen weights (up to 1.7-fold) were also evident at this dose.

In females, no effects on fertility endpoints were noted. Slight increases in the litter incidences of rib variations were noted at the HD, but the increases were not statistically significant. No effects were reported for ISIS 440670. The identified NOAEL for male and female fertility and embryofetal development was 87.5 mg/kg/wk.

A combined fertility and developmental study in CD-1 mice with ISIS 440670, an antisense inhibitor of the mouse *apoC-III* mRNA (study number 304801-AS08) administered SC every other day at dosages of 0, 10, or 25 mg/kg (equivalent to 0, 35, or 87.5 mg/kg/wk), effects were limited to decreases in platelet counts (reduced up to 22% at 25 mg/kg), decreased TG levels (reduced up to 67% at 25 mg/kg), and reductions in hepatic *apoC-III* mRNA (reduced up to 36% at 25 mg/kg) were observed in both sexes at both dosages. The latter two effects were related to the pharmacology of the compound. Postmortem examination revealed increases in spleen weights (up to 1.6-fold), increased kidney weights (up to 1.2-fold, and liver weights (up to 1.3-fold) at the 25 mg/kg dose. As with volanesorsen, slight increases in the incidence of rib variations were seen at both dose levels that did not reach statistical significance. There were no effects on fertility endpoints. Overall, under the conditions of the experiment, ISIS 440670 was well-tolerated up to 25 mg/kg (87.5 mg/kg/wk) following 10 weeks of treatment in males and 4 to 6 weeks of treatment in females. No adverse effects on male or female fertility or embryofetal development were observed at up to the top dose of 25 mg/kg (87.5 mg/kg/wk).

Embryofetal Development Study in the Rabbit

In an embryofetal development study, rabbits (study no. 304801-AS09) were administered volanesorsen SC at dosages of 3, 6, 15 mg/kg once every other day (equivalent to 10.5, 21, or 52.5 mg/kg/wk). Reduced feed consumption (18% lower during treatment period) with associated clinical observations of reduced/absent feces and reduced weight gain during the treatment (47% lower) and post-treatment (33% lower) periods in maternal animals at 52.5 mg/kg/wk. Postmortem examination revealed tan discoloration of the liver at 52.5 mg/kg/wk and increased weights of the kidney, liver, and spleen at all dosages (ranging from ~5% to 26%, although the effects were considered significant only at ≥ 21 mg/kg/wk. Abortions/delivery of non-viable fetuses were evident at 52.5 mg/kg/wk. At this dose, fetal weights were slightly lower (decreased up to 14%). There were no effects on gross, visceral, or skeletal development. The identified maternal NOAEL was 21 mg/kg/wk based on the reduced feed consumption, reduced weight gain, and abortion/reduced viable fetuses at 52.5 mg/kg/wk.

Pre- and Postnatal Toxicity Study in Mice

In a pre-/postnatal study, female CD-1 mice (study no. 304801-AS17) were administered volanesorsen SC at dosages of 3, 10 or 25 mg/kg every other day (equivalent to 10.5, 35, or 87.5 mg/kg/wk) during gestation followed by once weekly administration from parturition through postpartum day 21. An additional group was administered ISIS 440670 at 87.5 mg/kg/wk. Minimal effects were seen on maternal animals (body weights <6% lower; kidney, liver, and spleen weights increased <2-fold). The offspring at 87.5 mg/kg/wk weighed up to 15% less than concurrent controls and weights remained lower throughout the lifespan which contributed to delays in the age offspring reached various developmental landmarks. Delays of up to ~3 days occurred in the appearance of evidence of sexual maturity in females at all dosages of volanesorsen and with ISIS 440670. There were no effects on reproductive performance of F1 animals. The weights of various organs were also reduced in the F1 generation animals, but these

effects are considered secondary to the lighter body weights. The HD of 87.5 mg/kg/wk was considered the NOAEL for maternal animals based on the absence of an effect on reproductive function or the ability to raise a litter. For the F1 generation, 35 mg/kg/wk was considered the NOAEL based on the reduced weights observed throughout their lifespan at 87.5 mg/kg/wk.

13.3.4. Other Studies

Impurities/Degradants

Impurities were qualified in a 13-week impurity qualification study in mice and the 39-week repeat-dose toxicity study in monkeys.

13-Week Repeat-Dose Toxicity and Impurity Qualification Study in ICR Mice (Study No. 678354-AS06)

Olezarsen impurities were qualified in a 13-week repeat-dose toxicity study in Institute for Cancer Research mice in which the toxicity profile of two batches of olezarsen that had enriched impurity levels were compared to a representative batch of olezarsen that had not been enriched with impurities. The treatment groups (10/sex/group) received weekly SC doses of test article. Two dose levels (2.33 and 7 mg/kg/wk) of each formulation were administered. Animals in the olezarsen control group were dosed with test article prepared from drug substance CA678354-002 (purity, 91.3%) which was also used in Clinical Trial 3 (CS3). A vehicle control group was administered saline. Animals were terminated on Day 87. Mortality, clinical signs, body weight, food consumption, ophthalmic examinations, clinical pathology, and microscopic findings were evaluated to assess potential impurity-related toxicity.

Key Study Findings

- Target organs included liver, spleen, and injection site for all drug-treated groups.
- Microscopic findings were evident in the liver (single cell necrosis, mononuclear cell infiltration, nuclear degeneration/inclusions, cytomegaly / karyomegaly), spleen (extramedullary hematopoiesis), and injection site (mononuclear cell infiltration and basophilic granules). These effects were correlated with elevated liver enzymes (increases in ALT/AST of up to approximately 2-fold) and/or increase organ weights.
- In general, the incidences and severities were comparable between groups at the same dose, although the incidence and severity of single cell necrosis in the liver and extramedullary hematopoiesis in the spleen were slightly higher in the groups administered impurity-enriched olezarsen relative to that seen with olezarsen.
- Liver drug levels were comparable between all three test articles.

The drug-related effects observed in groups administered olezarsen with enhanced levels of impurities was considered similar to that observed in the group administered olezarsen without enhanced levels of impurities at each dose. Overall, there were no meaningful differences in the severity or incidence of the various findings at the evaluated dose levels. In conclusion, enhanced levels of impurities did not affect the established toxicity profile of olezarsen.

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The impurity levels considered qualified in this 13-week impurity qualification mouse study at the indicated toxicology coverage levels are shown in [Table 108](#).

Table 108. Qualification Levels for Impurities in Drug-Substance Batch CA 678354-002 Used in the 13-Week Impurity Qualification Study in Mice

^{(b) (4)} Impurity	Impurity Levels in Batch CA 678354-002 (%)	Toxicology Coverage (% of Clinical Dose) ^a
(b) (4)		

Source: Reviewer-created table based on data in Applicant Table 11 (Justification of Specifications in section 3.2.S.4.5)

^a Coverage calculated by multiplying the amount of the impurity (%) x the NOAEL (2.33 mg/kg/wk, equivalent to 9.32 mg/kg/month) divided by the MRHD of 80 mg/month, equivalent to 1.1 mg/kg/month for a 70-kg adult. Rounded to the nearest 0.1%.

Abbreviations: amu, atomic mass unit; ^{(b) (4)}; MRHD, maximum recommended human dose; NA, not applicable; ND, not determined; NOAEL, no observed adverse effect level; wk, week(s)

39-Week Monkey Study(Study No. 678354-AS02)

The levels of impurities qualified in this pivotal monkey study are summarized in [Table 109](#) below. The NOAEL from this study was 6 mg/kg/wk (equivalent to 24 mg/kg/month).

Table 109. Qualification Levels for Impurities in Drug-Substance Batch CA 678354-001 Used in the 39-Week Monkey Toxicology Study

^{(b) (4)} Impurity	Impurity Levels in Batch CA 678354-001 (%)	Toxicology Coverage (% of Clinical Dose)
(b) (4)		

Source: Reviewer-created table based on data in Applicant Table 2 (Justification of Specifications in section 3.2.S.4.5)

^a Coverage calculated by multiplying the amount of the impurity (%) x the NOAEL (6 mg/kg/wk, equivalent to 24 mg/kg/month) divided by the MRHD of 80 mg/month, equivalent to 1.1 mg/kg/month for a 70-kg adult. Rounded to the nearest 0.1%.

^b Reported on CofA as ^{(b) (4)} impurity although identity not confirmed by subsequent high-resolution MS analysis

Abbreviations: amu, atomic mass unit; CofA, certificate of analysis; ^{(b) (4)}; MRHD, maximum recommended human dose; MS, mass spectrometry; NA, not applicable; ND, not determined; NOAEL, no observed adverse effect level; wk, week(s)

In summary, the identified impurities in the above studies were qualified are at levels (b) (4) those being proposed for the drug substance specifications (see Section 9 of this review). From a toxicology perspective, there are no issues with the proposed specification levels for (b) (4) impurities in the drug substance.

14. Clinical Pharmacology

14.1. In Vitro Studies

Plasma Protein Binding

In Vitro Evaluation of the Extent of Plasma Protein Binding of ISIS 678354 in Human, Monkey, and Mouse Plasma by Ultrafiltration (Trial 678354-IS04)

The plasma protein binding of olezarsen was evaluated by an ultrafiltration method. Olezarsen at two nominal concentrations (5 and 150 µg/mL) in human, monkey, and mouse plasma was preincubated at 37°C for approximately 30 minutes without adjusting pH (pH in whole plasma ranged from 7.3 to 7.5) prior to ultra-centrifugation. The concentrations in plasma and ultrafiltrate were determined using a nuclease-dependent hybridization enzyme-linked immunosorbent assay (ELISA). Olezarsen is found to be highly bound to human plasma proteins (>99% bound) at concentrations of 5 and 150 µg/mL. The extent of plasma protein binding was similar across all species and between the two concentrations tested and determined to be ≥98%.

Distribution in Blood Cells

In Vitro Evaluation of Whole Blood and Plasma Concentration Ratio of ISIS 678354 (Olezarsen) in Human, Monkey, and Mouse (Trial 678354-IS11)

The blood to plasma distribution ratio of olezarsen was evaluated neat and at six different nominal concentrations (0, 0.01, 0.03, 0.1, 0.3, 1, and 3 µg/mL) in human whole blood, neat and at eight different nominal concentrations (0, 0.1, 0.3, 1, 3, 10, 30, 100, and 300 µg/mL) in monkey whole blood, and at seven different nominal concentrations (0, 0.1, 0.3, 1.00, 3.00, 10.0, and 30.0 µg/mL) in mouse whole blood. The blood to plasma ratio for olezarsen ranged from 0.73 to 0.98, 0.49 to 0.64, and 0.83 to 0.98 at concentrations tested in the human, monkey, and mice, respectively, suggesting that olezarsen distributes mostly in the plasma compartment.

14.1.1. Drug-Drug Interaction Studies

Study Related to Plasma Protein Binding Interactions

In Vitro Evaluation of Human Plasma Protein Binding of ISIS 678354 and its Interactions with Warfarin and Ibuprofen by Ultrafiltration (Trial 678354-IS06)

Warfarin and ibuprofen were selected for the evaluation of plasma protein-binding displacement with olezarsen because they are highly bound to albumin binding site I and site II, respectively. The substrate and displacer concentrations tested in this trial were 1 and 10 µg/mL for olezarsen, 3 and 30 µg/mL for warfarin, and 30 and 300 µg/mL for ibuprofen. The concentrations of

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olezarsen in plasma and ultrafiltrate were determined using a hybridization ECL assay, and concentrations of warfarin and ibuprofen were determined by high-performance liquid chromatography with tandem mass spectrometry.

The extent of plasma protein binding of olezarsen was similar with and without the presence of warfarin or ibuprofen, and the protein binding of warfarin and ibuprofen was similar with and without the presence of olezarsen. The percent displacement of olezarsen (as a substrate) by warfarin and ibuprofen (as displacers) or the percent displacement of warfarin or ibuprofen (as substrates) by olezarsen (as a displacer) was found to be negligible (<1%). These data suggest that no plasma protein-binding displacement is expected between olezarsen and other highly plasma protein-bound drugs.

Trials Related to Potential Involvement of Cytochrome P450 Isoforms

Cellular Uptake and In Vitro Evaluation of ISIS 678354 as Inhibitors of Cytochrome P450 Expression in Human Hepatocytes (Trial 678354-IS10)

Cytochrome P450 (CYP) inhibition study was performed by preincubating olezarsen for 30 minutes at concentrations ranging from 0.1 to 50 μ M in suspensions of cryopreserved cultured primary human hepatocytes, followed by the addition of a probe substrate for each CYP enzyme to initiate the metabolic reaction for 45 minutes for 1A2, 2B6, 2C9, 2D6, 3A4, and 90 minutes for 2C8, 2C19, 2E1.

Evaluations of the cellular uptake of olezarsen in cryopreserved cultured human primary hepatocytes was conducted with olezarsen at concentrations of 1, 10, and 50 μ M and an incubation time up to 120 minutes, where concentrations of olezarsen in cell pellets were determined using an LC-MS/MS method.

The results indicate that olezarsen up to 50 μ M does not inhibit the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Under the same experimental conditions, known inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 showed expected inhibition of enzyme activities, demonstrating that the hepatocyte inhibition experiment was appropriately performed.

Hepatocyte uptake of olezarsen occurred throughout the 120-minute incubation period, with an average intracellular concentration of 78.1 μ M after 60-minute incubation and 72.8 μ M after 120-minute incubation at 50 μ M of olezarsen in the incubation medium. These intracellular concentrations associated with hepatocytes are approximately 10-fold higher than the estimated steady-state level in the liver at the clinical dose of 80 mg once Q4W.

Taken together, results from this study demonstrate the lack of potential for olezarsen to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

In Vitro Assessment of Cytochrome P450 Induction Potential of ISIS 678354 in Plated Cryopreserved Human Primary Hepatocytes (Trial 678354-IS07)

The potential for olezarsen to act as an inducer of CYP1A2, CYP2B6, and CYP3A4 was evaluated in cryopreserved primary human hepatocytes using both the enzyme activities and corresponding mRNA levels. Human cryopreserved primary hepatocytes were treated with olezarsen at a concentration range of 0.1 to 50 μ M for 48 hours.

The results of the study demonstrated that olezarsen did not cause induction of CYP1A2, CYP2B6, or CYP3A4 at mRNA level in three donors, (b) (6), up to 50 μM except for CYP3A4 for donor (b) (6). In donor (b) (6), the maximal induction fold change in mRNA was 3.27-fold in CYP3A4 (5.41% of positive control rifampicin response) at 50 μM , with determined induction 50% effective concentration (EC_{50}) of 20 μM and maximum effect of 3.60-fold. At 10 μM , it showed less than 2-fold increase, considered as no effect. At the olezarsen media concentrations of 10 and 50 μM , the corresponding mean hepatocyte concentrations over the three time points (30, 60, and 120 minutes) were $35.6 \pm 3.98 \mu\text{M}$ and $72.2 \pm 13.5 \mu\text{M}$, respectively. These concentrations are significantly higher than the expected liver concentrations in patients (predicted based on data from the chronic monkey Study 678354-AS02) approximately by 4- and 9-fold, respectively. Thus, olezarsen is not an inducer of CYP3A4 at clinically relevant doses.

Taken together, results from this study demonstrate the lack of potential for olezarsen to induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant doses.

Trial Related to Potential Involvement of Major Drug Transporters

Assessment of ISIS 678354 as an Inhibitor or Substrate of Human Organic Anion Transporter (OAT)1, OAT3, Organic Cation Transporter (OCT)1, OCT2, Organic Anion Transporting Polypeptide (OATP)1B1, OATP1B3, Multidrug and Toxin Extrusion Protein (MATE)1, MATE2-K, Breast Cancer Resistance Protein (BCRP), P-glycoprotein (P-gp), and Bile Salt Export Pump (BSEP)-Mediated Transport (Trial 678354-IS08)

The potential for olezarsen to act as a substrate or inhibitor of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BSEP, BCRP, P-gp was evaluated at 10 μM and 100 μM of olezarsen, respectively. The transport of each probe substrate was determined by radiometric detection, while concentrations of olezarsen were determined using an LC-MS/MS method.

At a concentration of 100 μM of olezarsen, the mean percent inhibition ranged from -31.1% to 45.3% for all the transporters evaluated. Therefore, olezarsen is not considered an inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BSEP, BCRP, or P-gp. In the substrate assays at an olezarsen concentration of 10 μM , less than a 2-fold difference of uptake was observed in transporter-transfected cells compared with control cells for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP, suggesting that olezarsen is not a substrate for these transporters. For BCRP and P-gp, the permeability value and the efflux ratio were not determinable due to olezarsen concentrations in all receiver wells being below the lower limit of quantitation (LLOQ). However, given the extremely low B $\rightarrow$ A permeability ($<0.0287 \times 10^{-6} \text{ cm/s}$), olezarsen does not appear to be a substrate for BCRP or P-gp.

Taken together, results from this study demonstrate that olezarsen is not a substrate or inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP.

14.2. In Vivo Studies

A Placebo-Controlled, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of ISIS 678354, a GalNAc3 Conjugated 2'-MOE Chimeric Antisense Oligonucleotide Targeting ApoC-III, Administered Subcutaneously to Healthy Volunteers with Elevated Triglycerides (Trial ISIS 678354-CS1)

Objectives

The objectives of the study were to evaluate the safety and tolerability, PK, and effects on pharmacodynamics (PD), including plasma ApoC-III, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and very low-density lipoprotein cholesterol (VLDL-C), of single and multiple SC doses (both weekly and Q4W dosing regimens) of olezarsen in healthy volunteers with elevated TG.

Study Design

This was a Phase 1, double-blind, randomized, placebo-controlled, single-center, dose-escalation study. There were five ascending single-dose cohorts (N=8 per cohort, total randomized 6 active:2 placebo) with olezarsen doses of 10, 30, 60, 90, and 120 mg. The posttreatment evaluation period was Day 2 through Day 150 for the single-dose cohorts.

Volunteers in the multiple-dose cohorts were evaluated on weekly dosing for 6 weeks and Q4W for 3 months. The olezarsen doses were 15 mg (Cohort AA) and 30 mg (Cohort BB) for the weekly dosing cohorts (N=8 per cohort, total randomized 6 active:2 placebo) and 60 mg for the Q4W dosing cohort (Cohort CC; N=10, total randomized 6 active:4 placebo). The post-treatment evaluation period was Day 37 through Day 155 for the weekly multiple-dose cohorts and Day 86 through Day 204 for the Q4W multiple-dose cohort.

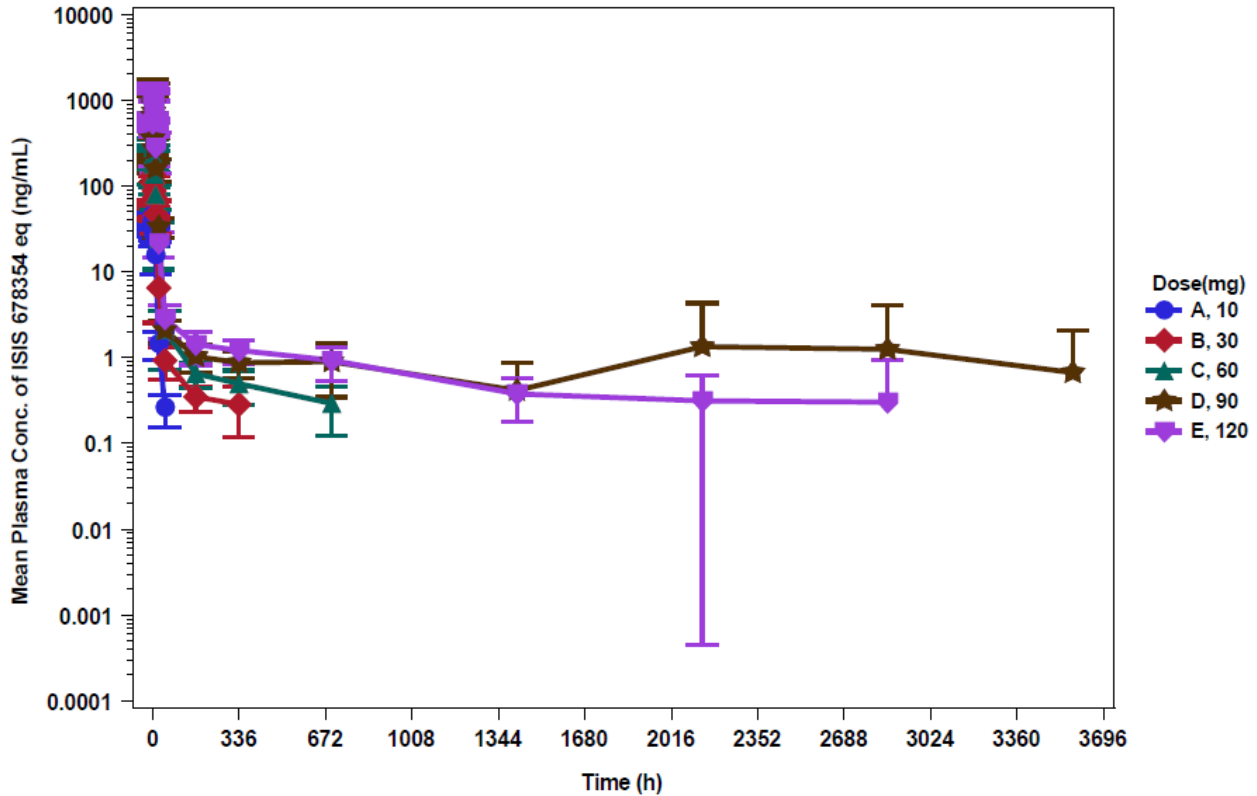
Results

PK

Following SC administration, olezarsen was rapidly absorbed into the systemic circulation, with median T_{max} ranging from 1 to 3 hours. Plasma olezarsen concentrations then declined over time in a multiphasic manner, with an initial rapid distribution phase dominating the plasma clearance followed by a much slower elimination phase with apparent terminal half-life ranging from 3 to 6 weeks ([Figure 44](#)). Plasma C_{max} and area under the concentration-time curve (AUC) increased slightly greater than dose proportionally over the dose range of 10 to 120 mg of olezarsen. No increase in C_{max} or AUC was observed after repeated weekly or Q4W administration ([Figure 45](#)). These data support time-invariant plasma kinetics for olezarsen.

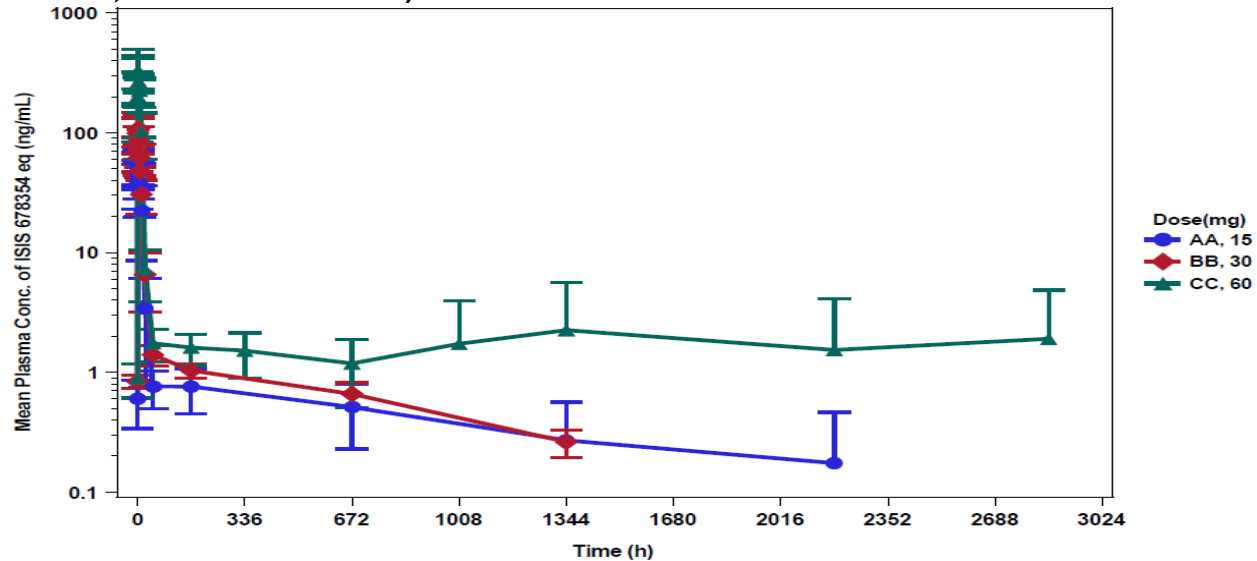
Rapid distributional clearance from plasma and limited recovery of full-length ASO in urine (<1% of administered dose over a 24-hour period) suggests that clearance from plasma occurred primarily by distribution to tissues, where the drug is metabolized to chain-shortened oligonucleotide metabolites prior to renal excretion.

Figure 44. Mean ($\pm$ SD) Plasma Concentrations of ISIS 678354-Equivalent vs. Time Following Single SC Dose Administration in the Single-Dose Cohorts, Trial CS1



Source: Figure 14.2.2.1.3 of ISIS 678354–CS1 study report
 Abbreviations:

Figure 45. Mean ($\pm$ SD) Plasma Concentrations of ISIS 678354-Equivalent vs. Time Following the Last SC Dose Administration on Day 36 (Weekly) or Day 85 (Every 4 Weeks) in the Multiple-Dose Cohorts, Trial ISIS 678354–CS1)

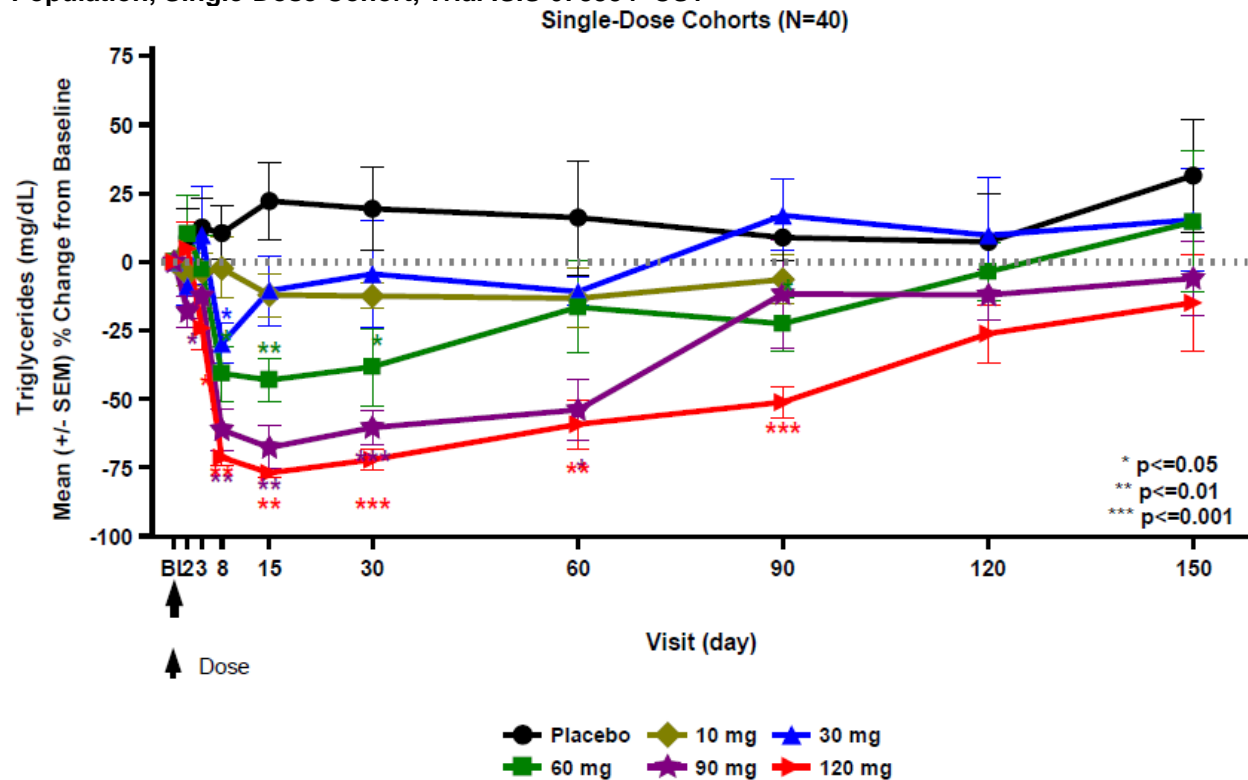


Source: Figure 14.2.2.2.5 of ISIS 678354–CS1 study report
 Abbreviations: conc., concentration; SC, subcutaneous; SD, standard deviation

PD

PD results showed dose-dependent sustained reductions in fasting plasma ApoC-III and TG levels, with particularly marked, statistically significant, reductions across the higher single-dose and all multiple-dose cohorts. Among the single-dose cohorts, reductions of 12%, 11%, 43%, 68%, and 77% (TG) and 4%, 32%, 65%, 78%, and 91% (ApoC-III) for the 10, 30, 60, 90, and 120 mg groups, respectively, were seen at Day 15, 2 weeks after dosing (Figure 46). The effects were sustained at Day 30, with reductions of 38%, 60%, and 72% (TG) and 58%, 72%, and 87% (ApoC-III) for the 60, 90, and 120 mg groups, respectively.

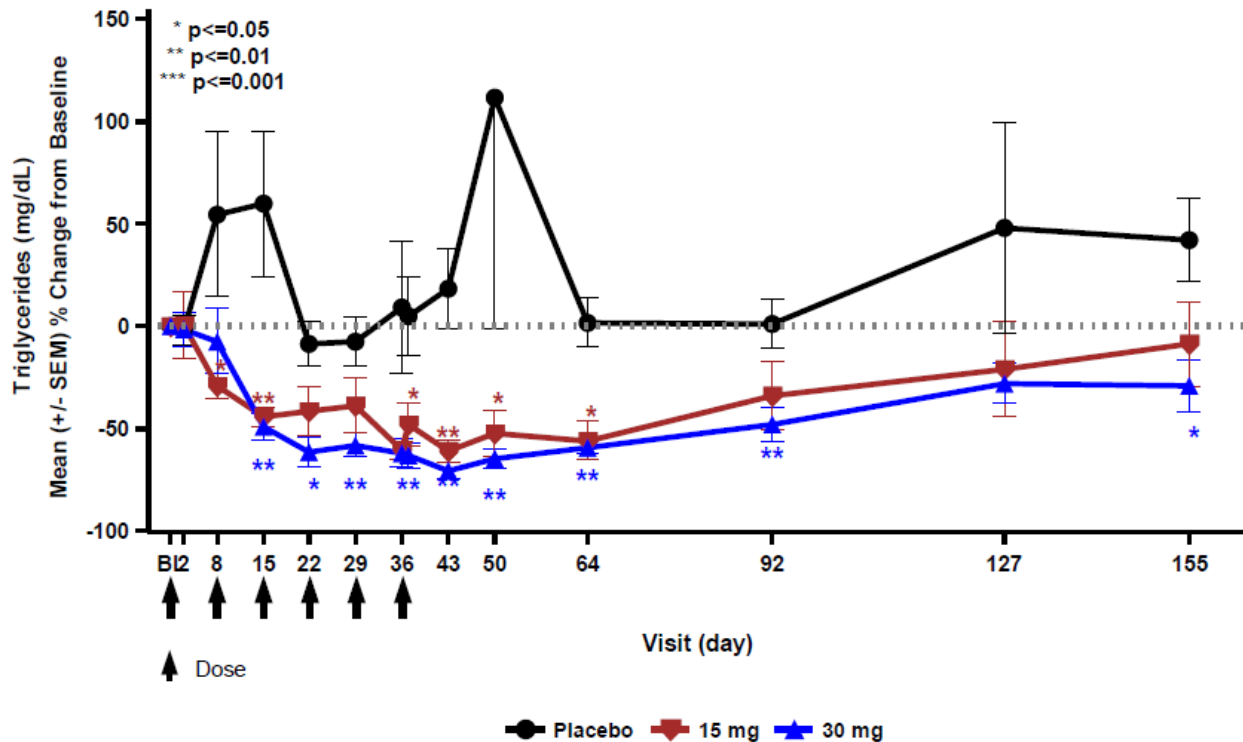
Figure 46. Mean ($\pm$ SEM) Percent Change From Baseline in Triglycerides (mg/dL) Over Time, Safety Population, Single-Dose Cohort, Trial ISIS 678354–CS1



Source: Figure 14.2.1.1.1c of ISIS 678354–CS1 study report
Abbreviations: BL, baseline; SEM, standard error of the mean

Among the weekly multiple-dose cohorts, reductions of 61% and 71% (TG) and 65% and 84% (ApoC-III) for the 15 and 30 mg groups were seen at Day 43 (one week after the last dose), respectively (Figure 47). The effects were sustained at Day 64, with reductions of 56% and 59% (TG) and 63% and 79% (ApoC-III) for the 15 and 30 mg groups. Similarly, increases in HDL-C concentrations of 50% to 56% from baseline were observed at Day 43 in the 15 and 30 mg weekly multiple-dose groups, respectively.

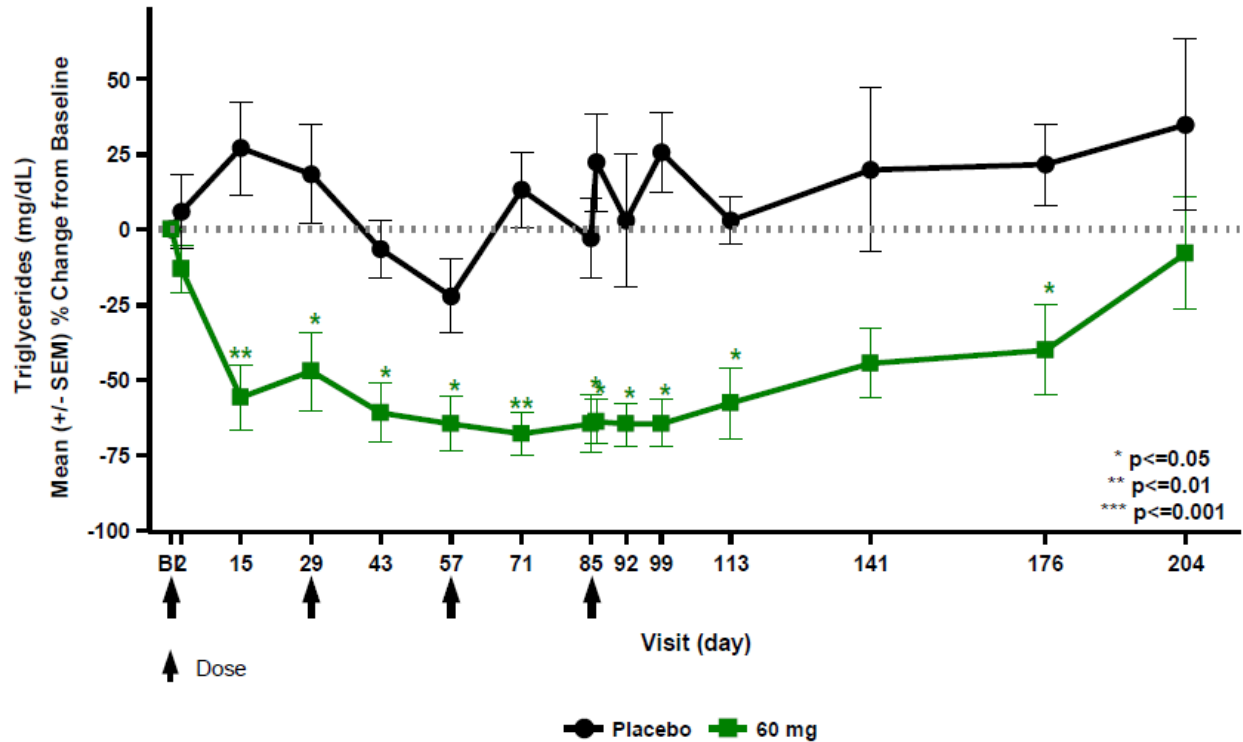
Figure 47. Mean ($\pm$ SEM) Percent Change From Baseline in Triglycerides (mg/dL) Over Time, Safety Population, Weekly Multiple-Dose Cohort, Trial ISIS 678354–CS1
 Weekly Multiple-Dose Cohorts (N=17)



Source: Figure 14.2.1.1.1c of ISIS 678354–CS1 study report
 Abbreviations: BL, baseline; SEM, standard error of the mean

Among the monthly multiple-dose cohort, reductions of 65% (TG) and 83% (ApoC-III) for the 60 mg group were seen at Day 92 (one week after the last dose) (Figure 48). The effects were sustained at Day 113, with reductions of 58% (TG) and 79% (ApoC-III) for the 60 mg group. In addition, increases in HDL-C concentrations of 76% from baseline were observed at Day 92 in the 60 mg monthly multiple-dose group. Among the multiple-dose cohorts, reductions in ApoB levels of approximately 20 to 30% were achieved, with no notable increases in any treatment group.

Figure 48. Mean ($\pm$ SEM) Percent Change From Baseline in Triglycerides (mg/dL) Over Time, Safety Population, Monthly Multiple-Dose Cohort, Trial ISIS 678354–CS1
Monthly Multiple-Dose Cohorts (N=10)



Source: Figure 14.2.1.1.1c of ISIS 678354–CS1 study report
Abbreviations: BL, baseline; SEM, standard error of the mean

A Randomized Double-Blind, Placebo-Controlled, Non-Confirmatory Study to Assess Safety, Tolerability, PK, and PD of Single Ascending and Multiple Doses of ISIS 678354 in Healthy Japanese Participants (Trial AKCEA-CS1)

Objectives

The objectives of the study were to assess the safety and tolerability (primary), PK (secondary), effects on fasting serum TGs and ApoC-III levels (exploratory), and immunogenicity of single and multiple SC dose administration of olezarsen in healthy Japanese participants.

Study Design

This was a randomized, placebo-controlled, participant and investigator-blinded, single ascending dose and multiple-dose study in healthy Japanese male and female participants conducted in the USA. In the single ascending dose portion, participants were randomized to olezarsen or placebo at each of three serial dose levels (30, 60, or 90 mg). For the multiple-dose part of this study, 60 mg of olezarsen or placebo was administered SC Q4W on Days 1, 29, 57, and 85.

Results

PK

Following single- or multiple-dose SC administration in healthy Japanese participants, olezarsen was absorbed rapidly into the systemic circulation, with median T_{max} ranging from 2 to 3 hours. After reaching C_{max}, plasma concentrations of olezarsen declined in a multi-phasic fashion, with a rapid disposition phase that dominated the plasma clearance, followed by a slower elimination phase with terminal elimination half-life of 8.2 to 27.5 days for single-dose cohorts and 30.8 days for the multiple-dose cohort. Of note, the half-life of 8.2 days observed following a single 30-mg dose of olezarsen is likely underestimated due to a majority of samples in the elimination phase being below the LLOQ. Plasma C_{max} and AUC increased slightly greater than dose proportionally over a dose range of 30 to 90 mg. There was no increase in plasma C_{max} or AUC after repeated Q4W administration of 60 mg olezarsen for 13 weeks.

The fraction of olezarsen excreted over 24 hours ranged from 0.0264% to 0.0741%, suggesting negligible renal elimination. Renal clearance over the first 24 hours also increased with dose and ranged from 6.24 mL/h to 12.0 mL/h.

PD

Following Single SC Administration of 30 mg, 60 mg, or 90 mg ISIS 678354

Following single SC doses of olezarsen at 30 mg, 60 mg, and 90 mg, mean percent decreases in TG levels from baseline were observed beginning on Day 3 and continued through Day 120. The most considerable effect of the administration of olezarsen on plasma TG levels compared with placebo appeared to occur on Day 15 postdose; the percentage differences (p-values) were -62.36% (0.124), -97.24% (0.021), and -83.78 (0.046) for the 30 mg, 60 mg, and 90 mg treatment groups, respectively. The percentage change in TG levels from baseline does not appear to be dose-dependent; the effect on TG levels appeared similar following single administration of either 60 mg or 90 mg ISIS 678354, and smaller following administration of 30 mg ISIS 678354.

Significant percentage decreases in ApoC-III levels following administration of ISIS 678354 compared with placebo were observed beginning on Day 8 in the 60 mg and 90 mg treatment groups and beginning on Day 15 in the 30 mg treatment group, with percentage differences (p-values) -61.02% (0.0004), -64.77% (0.0002), and -39.40 (0.0103), respectively. Significant decreases in ApoC-III levels continued to Day 90 postdose in the 60 mg and 90 mg treatment groups, and to Day 30 postdose in the 30 mg treatment group, with percentage differences (p-values) -39.84% (0.0023), -22.35% (0.0303), and -41.09 (0.0092), respectively. The most considerable effect of the administration of 30 mg, 60 mg, and 90 mg ISIS 678354 on plasma ApoC-III levels compared with placebo appeared to occur on Day 30, Day 8, and Day 15 postdose, respectively.

Following Multiple SC Administration of 60 mg ISIS 678354 Every 4 Weeks for a Total of Four Doses (Day 1, Day 29, Day 57, Day 85)

Following four SC doses (Day 1, Day 29, Day 57, and Day 85) of 60 mg olezarsen Q4W, mean percent decreases from baseline in TG levels were consistently observed from Day 2 to Day 204, 119 days after the last dose. The percentage change in TG from baseline ranged from -73.8% on

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Tryngolza (olezarsen sodium)

Day 92 to -31.7% on Day 204. The most considerable effect of the administration of ISIS 678354 on plasma TG levels compared with placebo appeared to occur on Day 113 where the percentage difference (p-value) was -71.96% (0.004).

Percentage decreases in ApoC-III levels from baseline results and differences in ApoC-III levels compared with placebo were consistently decreased from Day 2 to Day 204. The percentage change in ApoC-III from baseline ranged from -81.6% on Day 92 to -26.3% on Day 204. The most considerable effect of the administration of ISIS 678354 on plasma ApoC-III levels compared with placebo appeared to occur on Day 92 postdose where the percentage difference (p-value) was -81.63% (0.0002).

Immunogenicity

In single-dose cohorts, all participants who received placebo treatment had negative ADA results during the study. Overall, in the single-dose cohorts, three (15.0%) participants were assessed as ADA positive during the study (two [40.0%] participants in the 60 mg ISIS 678354 treatment group and one [16.7%] participant in the 90 mg ISIS 678354 treatment group). There was no association or trend between the incidence of ADA and dose level.

In multiple-dose cohorts, two (100%) participants who received placebo treatment had positive ADA results at Day 1 (titer of 50 for both participants), and three (50.0%) participants in the 60 mg ISIS 678354 treatment group were assessed as ADA positive at postdose time points during the study. There was a trend of increased ADA incidence with increased number of doses. No participants who tested ADA positive reported any TEAEs during the study.

A Single-Dose, Randomized, Open-Label, Two-Period Crossover Bioequivalence Study Comparing Two Subcutaneous Formulations: Vial and Autoinjector With Olezarsen, at Two Dose Levels, in Healthy Adult Participants (Trial ISIS 678354-CS20)

Objectives

Primary Objective

The primary objective of this study was to assess the bioequivalence of olezarsen between two SC formulations at two dose levels: (1) autoinjector ((b) (4) mg/mL) and vial (100 mg/mL) at the 50 mg dose; and (2) autoinjector (100 mg/mL) and vial (100 mg/mL) at the 80 mg dose, in healthy adult participants.

The primary endpoint was to assess whether the bioequivalence at each dose level calculated at the 90% CI for the ratio of geometric means (GMs) for AUC_{0-336h} and C_{max} for olezarsen fell within 80.00% to 125.00%.

Exploratory Objective

The exploratory objective of this study was to assess serum ApoC-III reduction from baseline over time (pre-dose through 91 days post-last dose).

Study Design

This was a Phase 1, single-dose, randomized, open-label, 2-period, 2-sequence, 2-treatment, 2-way crossover, BE study that evaluated two dose levels of olezarsen (50 mg and 80 mg).

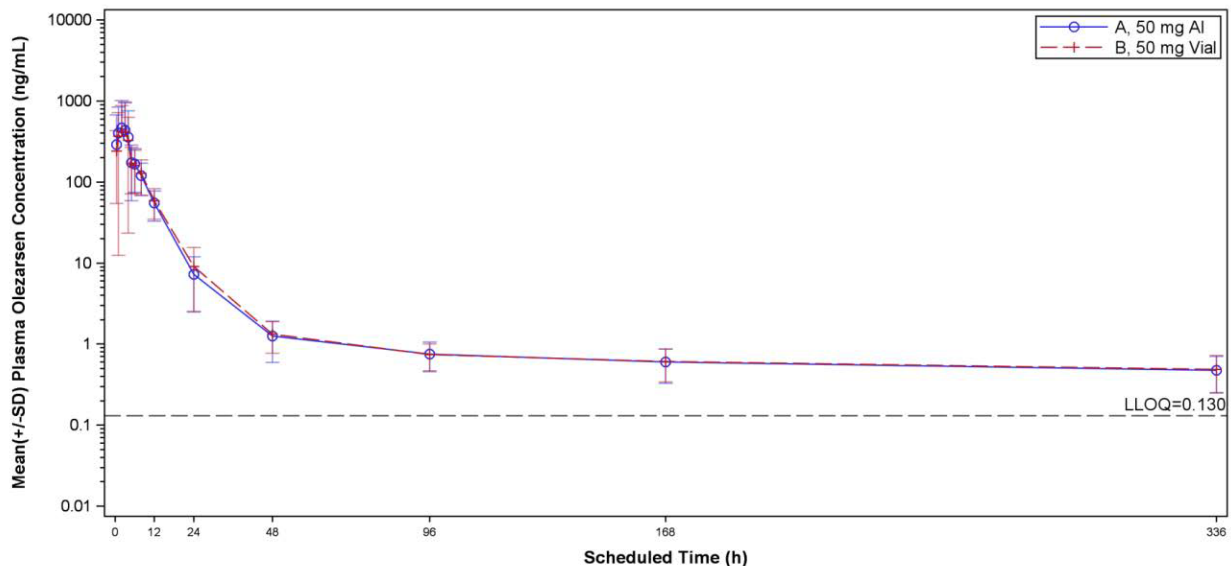
Following an up to 28-day screening period, 104 eligible participants were randomized to two dose groups (50 mg or 80 mg). There was a 28- to 42-day washout period between Day 1 of treatment period 1 and Day 1 of treatment period 2 to avoid PK carry over effects of the preceding treatment. Blood samples for PK analyses were collected at pre-dose (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 96, 168, and 336 hours postdose in each of the two treatment periods and during the post-treatment follow-up period (28, 56, and 91 days post-last dose). Blood samples for PD analysis (i.e., serum ApoC-III and serum TGs) were collected during treatment periods 1 and 2 on Day -1, Day 1 (pre-dose), Day 8, and Day 15 and the post-treatment follow-up period (28, 56, and 91 days post-last dose).

Results

PK

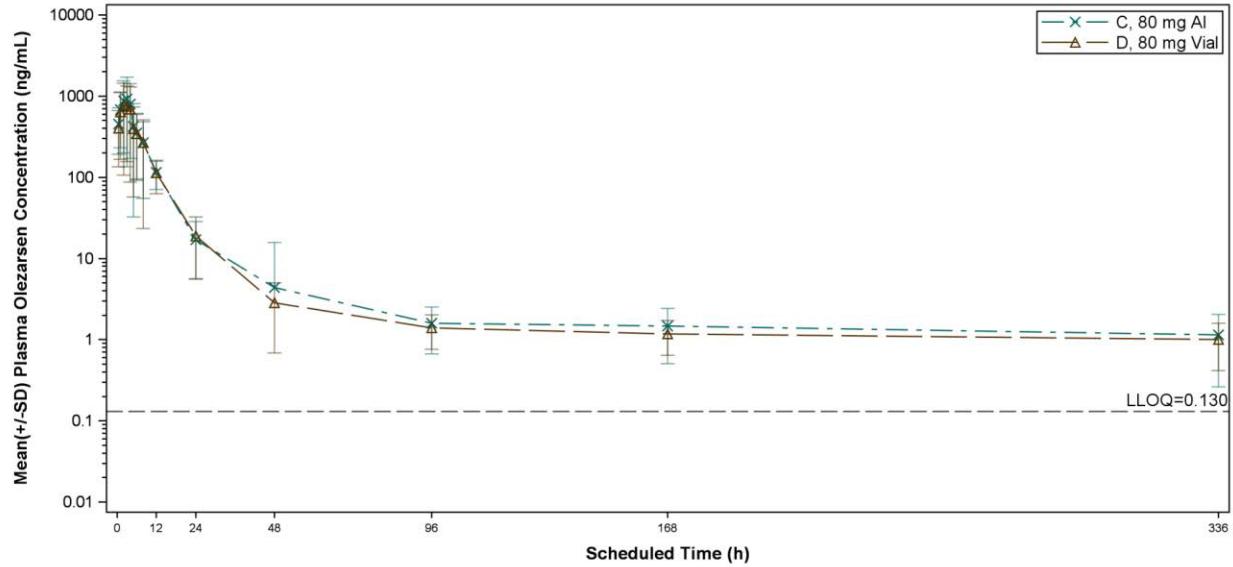
The PK exposures after administration of the four treatments are presented in [Figure 49](#) (olezarsen 50 mg, semi-log scale), [Figure 50](#) (olezarsen 80 mg, semi-log scale), and are summarized in [Table 110](#). The geometric least square (LS) means and ratios for olezarsen AUC_{0-336h} and C_{max} comparing the autoinjector to the vial at the 50 and 80 mg dose levels are summarized in [Table 111](#).

Figure 49. Plot of Mean ($\pm$ SD) Plasma Olezarsen Concentrations by Treatment on Semilogarithmic Scale – Olezarsen 50 mg, PK Population, Trial CS20



Source: ISIS 678354-CS20 Clinical Study Report, Figure 14.2.1.2
Abbreviations: AI, autoinjector; LLOQ, lower limit of quantitation; PK, pharmacokinetics; SD, standard deviation

Figure 50. Plot of Mean ($\pm$ SD) Plasma Olezarsen Concentrations by Treatment on Semilogarithmic Scale – Olezarsen 80 mg, PK Population, Trial CS20



Source: ISIS 678354-CS20 Clinical Study Report, Figure 14.2.1.6
Abbreviations: AI, autoinjector; LLOQ, lower limit of quantitation; PK, pharmacokinetics; SD, standard deviation

Table 110. Plasma Pharmacokinetics of the Four Olezarsen Presentations, PK Population, Trial CS20

Olezarsen Presentation	Dose (mg)	N	Median (Min, Max)	Geometric Mean (CV [%])		
			T _{max} (h)	C _{max} (ng/mL)	AUC _{0-336h} (h*ng/mL)	AUC _{0-24h} (h*ng/mL)
Treatment A (AI)	50	49	2.00 (1.00, 4.00)	374 (71.1)	2741 (47.0)	2468 (50.1)
Treatment B (vial)	50	50	2.00 (1.00, 4.00)	344 (80.7)	2719 (43.1)	2421 (47.6)
Treatment C (AI)	80	51	3.00 (1.00, 4.00)	764 (81.7)	5733 (49.4)	5042 (55.4)
Treatment D (vial)	80	48	2.00 (0.50, 6.00)	663 (84.3)	5231 (50.0)	4631 (55.7)

Source: ISIS 678354-CS20 Clinical Study Report, Table 14.2.2.1, Table 14.2.2.4
Abbreviations: AI, autoinjector; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; max, maximum; min, minimum; T_{max}, time to maximum concentration

Bioequivalence Evaluation for Olezarsen 50 mg

The calculated 90% CIs for the olezarsen 50 mg autoinjector (test, Treatment A) and the olezarsen 50 mg vial (reference, Treatment B) ratios of geometric mean for AUC_{0-336h} and C_{max} fell within 80.00% to 125.00%, consistent with PK bioequivalence between the two formulations.

Table 111. Analysis of Relative Bioavailability and Bioequivalence of Plasma Olezarsen PK Parameters – Olezarsen 50 mg and 80 mg, PK Statistical Population, Trial CS20

Olezarsen 50 mg							
PK Parameter	PK Unit	Olezarsen 50 mg Autoinjector (Treatment A)		Olezarsen 50 mg Vial (Treatment B)		Ratio of Adj Geo Means ^a (Olezarsen 50 mg Autoinjector [Treatment A]/ Olezarsen 50 mg Vial [Treatment B]) (%)	90% CI for Ratio ^b (%)
		n	Adj Geo Mean ^a	n	Adj Geo Mean ^a		
AUC _{0-336h}	h*ng/mL	47	2825	47	2691	104.99	(101.66, 108.43)
C _{max}	ng/mL	47	383	47	330	116.07	(108.63, 124.02)
Olezarsen 80 mg							
PK Parameter	PK Unit	Olezarsen 80 mg Autoinjector (Treatment C)		Olezarsen 80 mg Vial (Treatment D)		Ratio of Adj Geo Means ^a (Olezarsen 80 mg Autoinjector [Treatment C] / Olezarsen 80 mg Vial [Treatment D]) (%)	90% CI for Ratio ^b (%)
		n	Adj Geo Mean ^a	n	Adj Geo Mean ^a		
AUC _{0-336h}	h*ng/mL	47	5843	47	5226	111.80	(106.96, 116.86)
C _{max}	ng/mL	47	789	47	663	118.94	(108.83, 129.99)

Source: ISIS 678354-CS20 Clinical Study Report, Table 14.2.3.1 and Table 14.2.3.3

Abbreviations: adj, adjusted; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; geo, geometric; PK, pharmacokinetics

Bioequivalence Evaluation for Olezarsen 80 mg

The ratio of adjusted GMs and 90% CI for AUC_{0-336h} between olezarsen 80 mg autoinjector (test, Treatment C) and olezarsen 80 mg vial (reference, Treatment D) were 111.80% and 106.96%, 116.86%, respectively, and the 90% CI was contained within 80.00% to 125.00%. For C_{max}, the ratio of adjusted GMs and 90% CI were 118.94% and 108.83%, 129.99%, respectively, with upper bound exceeding the prespecified range of 80.00% to 125.00% by 4.99%.

PD Analyses for Olezarsen 50 mg and 80 mg:

Analysis of percent change in pharmacodynamic measurements during treatment period 1 indicated that the 90% CI for difference of LS means between the autoinjector and the vial encompasses 0, indicating there were no meaningful differences between the two treatments (autoinjector and vial) in the reduction of ApoC-III and TG levels following olezarsen

administration for both the 50 mg and 80 mg dose groups (Table 112 and Table 113). Data from treatment period 1 were used, as this avoided a pharmacodynamic carry over effect from treatment period 1 to treatment period 2 since substantial reductions of ApoC-III and TG were observed on treatment period 2, Days -1 and 1.

Table 112. Analysis of Percent Change in Pharmacodynamic Measurements During Treatment Period 1 – Olezarsen 50 mg, Pharmacodynamic Population, Trial CS20

Parameter	Olezarsen 50 mg Autoinjector (Treatment A)		Olezarsen 50 mg Vial (Treatment B)		Difference of LS Means (Olezarsen 50 mg Autoinjector [Treatment A] – Olezarsen 50 mg Vial [Treatment B])	90% CI for Difference of LS Means
	Visit	n	LS Mean (SE)	n		
Apolipoprotein C-III						
Period 1 Day 8	26	-55.23 (4.372)	26	-53.43 (4.374)	-1.79	(-12.07, 8.48)
Period 1 Day 15	26	-59.65 (4.372)	25	-55.39 (4.431)	-4.26	(-14.60, 6.08)
Period 2 Day -1	17	-45.54 (4.960)	17	-53.27 (4.971)	7.73	(-3.91, 19.36)
Period 2 Day 1 (Pre-dose)	24	-49.46 (4.476)	23	-48.82 (4.542)	-0.64	(-11.22, 9.95)
Triglycerides						
Period 1 Day 8	26	-28.30 (4.372)	26	-26.56 (4.371)	-1.74	(-11.99, 8.52)
Period 1 Day 15	26	-32.12 (4.372)	25	-31.60 (4.448)	-0.52	(-10.86, 9.82)
Period 2 Day -1	17	-28.40 (5.194)	17	-31.82 (5.201)	3.43	(-8.75, 15.60)
Period 2 Day 1 (Pre-dose)	24	-30.81 (4.516)	23	-32.68 (4.603)	1.87	(-8.82, 12.55)

Source: ISIS 678354-CS20 Clinical Study Report, Table 14.2.5.3

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error

Table 113. Analysis of Percent Change in Pharmacodynamic Measurements During Treatment Period 1– Olezarsen 80 mg, Pharmacodynamic Population, Trial ISIS 678354-CS20

Parameter	Olezarsen 80 mg Autoinjector (Treatment C)		Olezarsen 80 mg Vial (Treatment D)		Difference of LS Means (Olezarsen 80 mg Autoinjector [Treatment C] – Olezarsen 80 mg Vial [Treatment D])	90% CI for Difference of LS Means
	n	LS Mean (SE)	n	LS Mean (SE)		
Apolipoprotein C-III						
Period 1 Day 8	25	-75.24 (2.697)	26	-75.25 (2.646)	0.01	(-6.30, 6.31)
Period 1 Day 15	24	-75.47 (2.714)	26	-78.19 (2.646)	2.72	(-3.60, 9.05)
Period 2 Day -1	16	-66.28 (2.919)	20	-75.50 (2.764)	9.23	(2.53, 15.92)
Period 2 Day 1	23	-65.78 (2.736)	25	-72.71 (2.663)	6.93	(0.56, 13.30)
Triglycerides						
Period 1 Day 8	25	-32.83 (6.049)	26	-36.14 (5.933)	3.31	(-10.71, 17.33)
Period 1 Day 15	25	-39.63 (6.049)	26	-44.01 (5.933)	4.38	(-9.64, 18.40)
Period 2 Day -1	16	-41.50 (7.403)	20	-36.11 (6.673)	-5.38	(-21.87, 11.10)
Period 2 Day 1	23	-45.63 (6.287)	25	-45.42 (6.039)	-0.21	(-14.64, 14.22)

Source: ISIS 678354-CS20 Clinical Study Report, Table 14.2.5.4

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error

Conclusions

- The primary endpoint of BE between the autoinjector and the vial presentations based on AUC_{0-336h} was achieved for both olezarsen 50 mg and 80 mg dose levels.
- Bioequivalence between the autoinjector and the vial presentations based on C_{max} was achieved for the olezarsen 50 mg dose level. For the olezarsen 80 mg dose level, the geometric mean ratio 90% CI for C_{max} was slightly above the standard upper CI limit for BE (80.00% to 125.00%), by 4.99%; however, this small difference is not clinically relevant due to the short duration around C_{max} during which plasma concentration versus time profiles

showed a small difference, and the rest of the concentration-time profiles were nearly superimposable.

- The PD effect of olezarsen on ApoC-III and TG reduction was similar between autoinjector and vial presentations at either the olezarsen 50 mg or 80 mg dose, which also supports that the small difference in C_{max} at the olezarsen 80 mg dose is not clinically relevant.
- There were no clinically meaningful differences in safety profile and ISRs between the autoinjector and vial presentations for olezarsen at either olezarsen 50 mg or 80 mg dose.

14.3. Bioanalytical Method Validation and Performance

Quantification of Olezarsen Concentrations in Human Plasma

Briefly, olezarsen was quantitatively measured directly from human plasma using a hybridization ECL assay. In this assay, samples were treated with proteinase K to mitigate potential interference from ADAs. Olezarsen in samples was hybridized to a complementary capture probe, which was biotinylated on the 5'-end. The hybridized olezarsen was then immobilized on a streptavidin-coated MesoScale Discovery (MSD) plate. A detection probe labeled with ruthenium (MSD-Tag) on the 3'-end is added to the plate to bind to the free portion of olezarsen. After addition of read buffer, the plate was read in an MSD Sector PRTM 600 plate reader.

The method validation evaluated the quantification range, accuracy, precision, potential interference, and cross-reactivity to selected putative metabolites, hook effect, dilutional linearity, selectivity, matrix effect, hemolysis and lipemia effects, potential ADA interference, quantification of unconjugated olezarsen (ISIS 304801, volanesorsen) and total full-length ASO, and stability. The validation range was 0.015 nM (0.13 ng/mL) to 20 nM (173.7 ng/mL), with the low end of the range defining the LLOQ.

Validation results demonstrated that the method was suitable for quantification of olezarsen and unconjugated olezarsen. The method performance over the validation is provided in [Table 114](#).

Table 114. Summary of Method Performance for Quantification of Olezarsen in Human Plasma (ICD 624)

Parameter	Results
Report No.	678354-MV04 678354-MV04 Addendum 1 678354-MV04 Addendum 2
Clinical studies supported	AKCEA-CS1 (Phase 1), ISIS 678354-CS1 (Phase 1), ISIS 678354-CS2 (Phase 1), ISIS 678354-CS3 (Phase 3), ISIS 678354-CS7 (Phase 3), ISIS 678354-CS8 (Phase 2b), ISIS 678354-CS13 (Phase 3), ISIS 678354-CS20 (Phase 1)
Materials used for standard calibration curve and concentration	Olezarsen (Bioanalytical Solution Standard), Lot BSS-678354-01: 0.015, 0.03, 0.06, 0.12, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, and 20.0 nM (0.13, 0.26, 0.52, 1.04, 2.17, 4.34, 8.68, 21.71, 43.42, 86.85, and 173.7 ng/mL, respectively)

NDA 218614
Tryngolza (olezarsen sodium)

Parameter	Results
Validated assay range	0.015 nM (0.13 ng/mL) to 20.0 nM (173.7 ng/mL)
Assay method	Hybridization ECL assay
Material used for QCs and concentration	Olezarsen (Bioanalytical Solution Standard); Lot BSS-678354-01: 0.015, 0.03, 0.045, 1.5, 15, 18, and 20 nM
Source and lot of reagents	Dipotassium EDTA human plasma: (b) (4) Water: Milli-Q 10× Dulbecco's PBS: (b) (4) Sodium Phosphate, dibasic: (b) (4) Sodium Chloride: (b) (4) Trizma base: (b) (4) Tween-20: (b) (4) Blocker A: (b) (4) Diluent 100: (b) (4) 4× Read Buffer T: (b) (4) Hydrochloric Acid (HCl): (b) (4) (b) (4) buffer G2: (b) (4) Proteinase K: (b) (4)
Regression model and weighting	Four-parameter logistic, 1/response ²
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 11 Cumulative accuracy (% bias) from LLOQ to ULOQ: -2.44% to 2.78% Cumulative precision (% CV) from LLOQ to ULOQ: 1.63% to 4.28%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs: 2.46% to 7.78% Inter-batch %CV: ≤ 9.03% Total error (TE): ≤ 16.40%
Selectivity and matrix effect	Acceptable with 10 out of 10 blank sample lots meeting the acceptance criteria. Acceptable with 10 out of 10 sample lots fortified at the LLOQ level, and 10 out of 10 sample lots fortified at the high QC level, meeting the acceptance criteria.
Interference and specificity	The percentage cross-reactivity of ISIS 489608 (19-mer), ISIS 489609 (10-mer), and ISIS 489611 (5-mer) with olezarsen is 130.7%, < 0.100%, and < 0.100%, respectively. No interference from metabolites ISIS 489609 (10-mer) and ISIS 489611 (5-mer) up to 3.000 nM (20% of olezarsen concentration), and metabolite ISIS 489608 (19-mer) at 5% of olezarsen, on the quantification of olezarsen in human plasma. However, there is an interference from metabolite ISIS 489608 (19-mer) at 0.009 nM (20% of olezarsen concentration) when in the presence of 0.045 nM olezarsen and at 3 nM (20% of olezarsen concentration) when in the presence of 15 nM olezarsen. Therefore, any interpretation of plasma concentrations of olezarsen will need to consider the type and level of metabolites present when accounting for potential interference. There was no interference on the quantification of olezarsen in K2EDTA human plasma when fortified with ADA at 10 µg/mL.
Hemolysis effect	No effect from hemolysis on the quantification of olezarsen
Lipemic effect	No effect from lipemia on the quantification of olezarsen
Dilution linearity and hook effect	200-, 2000-, and 20,000-fold dilution of 2000 nM Hook effect: No apparent prozone or "hook" effect was observed at concentrations up to 54,117 nM
Bench-top/Process stability	25 hours at room temperature

Parameter	Results
Freeze-Thaw stability (after 4 freeze-thaw cycles)	5 cycles thawed at room temperature
Long-Term storage	116 days at -25 °C 1467 days at -80 °C

Source: CSRs Study No. 678354-MV04, Study No. 678354-MV04-Addendum 1, Study No. 678354-MV04-Addendum 2
Abbreviations: ADA, antidrug antibody; CV, coefficient of variation; ECL, electrochemiluminescence; LLOQ, lower limit of quantitation; PBS, phosphate-buffered saline; QC, quality control; TE, total error; ULOQ, upper limit of quantitation

All samples analyzed within the 1467 days demonstrated long-term storage stability in human plasma containing dipotassium EDTA at -80°C. The incurred sample reanalysis was performed in 6.65 to 10.86% of samples across the clinical studies, and 88.8% to 98.5% of these samples met the prespecified acceptance criterion.

Quantification of Olezarsen Concentrations in Human Urine

Olezarsen in human urine was quantitatively measured using a partially validated hybridization ELISA. Olezarsen was hybridized to a complementary cutting probe (678354LNARP), which was biotinylated at the 5'-end of the sequence and had digoxigenin at the 3'-end. The hybridized solution was then placed in a NeutrAvidin-coated ELISA plate. After binding had taken place, S1 nuclease was added to digest any unhybridized probes. An anti-digoxigenin antibody conjugated to alkaline phosphatase was used to detect the hybridized analyte by binding to the digoxigenin label. AttoPhos was used as a substrate for fluorometric readout. Fluorescence intensity was determined using a fluorescent plate reader. The hybridization ELISA is capable of quantifying olezarsen and unconjugated olezarsen (ISIS 304801) equivalently; therefore, the assay is capable of quantifying total full-length ASOs of olezarsen, using olezarsen for calibration. The method performance over the validation is provided in [Table 115](#).

Table 115. Summary of Method Performance for Quantification of Olezarsen in Urine

Parameter	Results
Report No.	678354-MV05
Clinical studies supported	AKCEA-CS1 (Phase 1), ISIS 678354-CS1 (Phase 1)
Materials used for standard calibration curve and concentration	Olezarsen: 0.15, 0.3, 0.5, 1, 2.5, 5, 10, and 20 nM (1.303, 2.605, 4.342, 8.685, 21.71, 43.42, 86.85, and 173.7 ng/mL, respectively)
Validated assay range	0.15 nM (1.3 ng/mL) to 20.0 nM (173.7 ng/mL)
Assay method	Hybridization ECL assay
Material used for QCs and concentration	Olezarsen: 0.15, 0.3, 0.45, 3, 15, 18, and 20 nM (1.3, 2.61, 3.91, 26.05, 130.3, 156.3, and 173.7 ng/mL, respectively)
Source and lot of reagents	Olezarsen (olezarsen working solution standard); Lot WSS-678354-01 Olezarsen (olezarsen bioanalytical solution standard); Lot BSS-678354-01 Volanesorsen (unconjugated olezarsen bioanalytical solution standard); Lot WSS-304801-02 678354LNARP (olezarsen cutting probe; Lot 618977 [4352:43-44 and 4398:62])
Regression model and weighting	Four-parameter logistic, 1/response ²

Parameter	Results
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 8 Cumulative accuracy (% bias) from LLOQ to ULOQ: -5.80% to 7.71% Cumulative precision (% CV) from LLOQ to ULOQ: 2.12% to 6.11%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs: -14.9% to 170% Inter-batch %CV: ≤ 319% Total error (TE): ≤ 38.1%
Interference and specificity	The % cross-reactivity of the following: ISIS 489608 (19-mer) without olezarsen was 83.3% ISIS 489609 (10-mer) without olezarsen was < 1.0% ISIS 489611 (5-mer) without olezarsen was < 1.0%. There was no interference from the metabolite ISIS 489608 (19-mer) on the quantification of olezarsen in human urine at concentrations up to 0.03 nM (20% of olezarsen concentration) when in the presence of 0.15 nM olezarsen, and at concentrations up to 3.0 nM (20% of olezarsen concentration) when in the presence of 15.0 nM olezarsen. There was no interference from the metabolite ISIS 489609 (10-mer) on the quantification of olezarsen in human urine at concentrations up to 0.3 nM (200% of olezarsen concentration) when in the presence of 0.15 nM olezarsen, and at concentrations up to 30.0 nM (200% of olezarsen concentration) when in the presence of 15.0 nM olezarsen. There was no interference from the metabolite ISIS 489611 (5-mer) on the quantification of olezarsen in human urine at concentrations up to 0.6000 nM (400% of olezarsen concentration) when in the presence of 0.15 nM olezarsen, and at concentrations up to 60.0 nM (400% of olezarsen concentration) when in the presence of 15.0 nM olezarsen.
Dilution linearity and hook effect	200-, 500-, and 4000-fold dilution of 2000 nM 100-, 400-, and 2000-fold dilution of 1000 nM Hook effect: No apparent prozone or hook effect was observed at concentrations up to 54,117 nM.

Source: CSR Study No. 678354-MV05

Abbreviations: CV, coefficient of variation; ECL, electrochemiluminescence; LLOQ, lower limit of quantitation; PBS, phosphate-buffered saline; QC, quality control; TE, total error; ULOQ, upper limit of quantitation

The incurred sample reanalysis was performed in 35.71% of the total samples, and 100% of the incurred sample reanalysis samples met the prespecified criteria.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

A validated qualitative ELISA method was used for the detection and assessment of anti-olezarsen antibodies in human plasma in a multi-tiered approach: (1) screening assay, which identifies initial positive or negative samples; (2) confirmation assay, which assesses specificity of the positive screen samples by free-drug competition; and (3) titration assay, which estimates the level of antibody for the confirmed positive samples. Assay sensitivity was determined using affinity purified rabbit anti-olezarsen IgG and was defined as 9.65 ng/mL and 39.1 ng/mL in neat human plasma for the screening and confirmatory assays, respectively. The assay's ability to

detect anti-olezarsen antibodies in the presence of circulating olezarsen (drug tolerance) was determined to be 39.1 ng/mL of antibody in the presence of up to 4000 ng/mL of olezarsen. No neutralizing assay was developed.

ADA sampling was obtained from patients with FCS from Trial ISIS 678354-CS3 on Days 1, 15, 29, 57, 85, 169, 253, 365, and follow-up visit. Treatment-emergent (treatment-induced and treatment-boosted) ADAs against olezarsen were detected in 38.1% (8/21) of patients in the 50 mg olezarsen group, 45.5% (10/22) of patients in the 80 mg olezarsen group, and 0% (0/23) of patients who received placebo. As a reference, the proportion of patients with ADAs detected at baseline were 38.1% (8/21), 27.3% (6/22), and 43.5% (10/23) of patients in the 50 mg olezarsen, 80 mg olezarsen, and pooled placebo groups, respectively; an overall baseline positive rate of 36.4% (24/66). Of note, 26 out of the 66 patients in the study had previous treatment with volanesorsen. The baseline positive rate was 53.8% (14/26) and 25.0% (10/40) in patients with and without previous volanesorsen treatment, respectively.

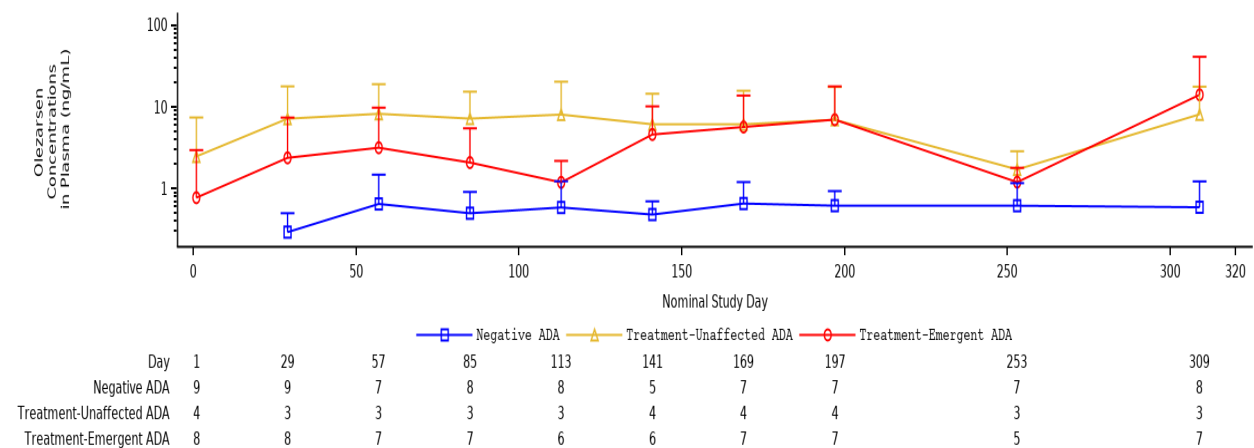
Impact of Immunogenicity on Pharmacokinetics

Higher plasma olezarsen C_{trough} levels were consistently observed in ADA-positive patients (either treatment-unaffected or treatment-emergent ADA) compared with ADA-negative patients across olezarsen clinical studies. In Trial ISIS 678354-CS3 specifically, mean trough plasma olezarsen concentrations in the olezarsen 80 mg group were elevated up to approximately 10-fold in FCS patients with treatment-unaffected and treatment-emergent ADA relative to ADA-negative patients, and the corresponding elevations for patients in the olezarsen 50 mg group were up to approximately 5-fold relative to ADA-negative patients.

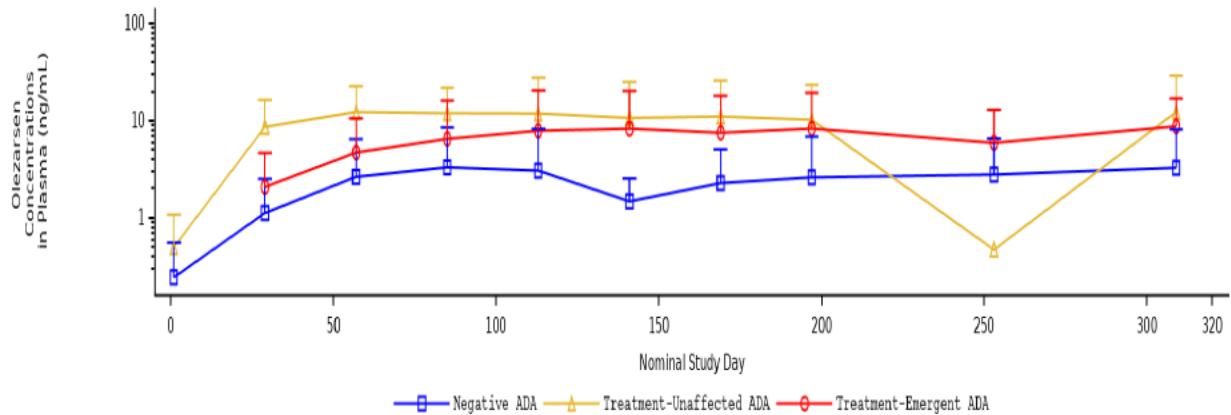
The mean ($\pm$ SD) olezarsen trough plasma concentrations over time stratified by ADA category in patients with FCS in Trial ISIS 678354-CS3 are presented in [Figure 51](#).

Figure 51. Mean ($\pm$ SEM) Olezarsen Trough Plasma Concentrations Over Time by Antidrug Antibody Status in Patients With Familial Chylomicronemia Syndrome, Trial ISIS 678354-CS3

Olezarsen 50 mg Q4W



Olezarsen 80 mg Q4W



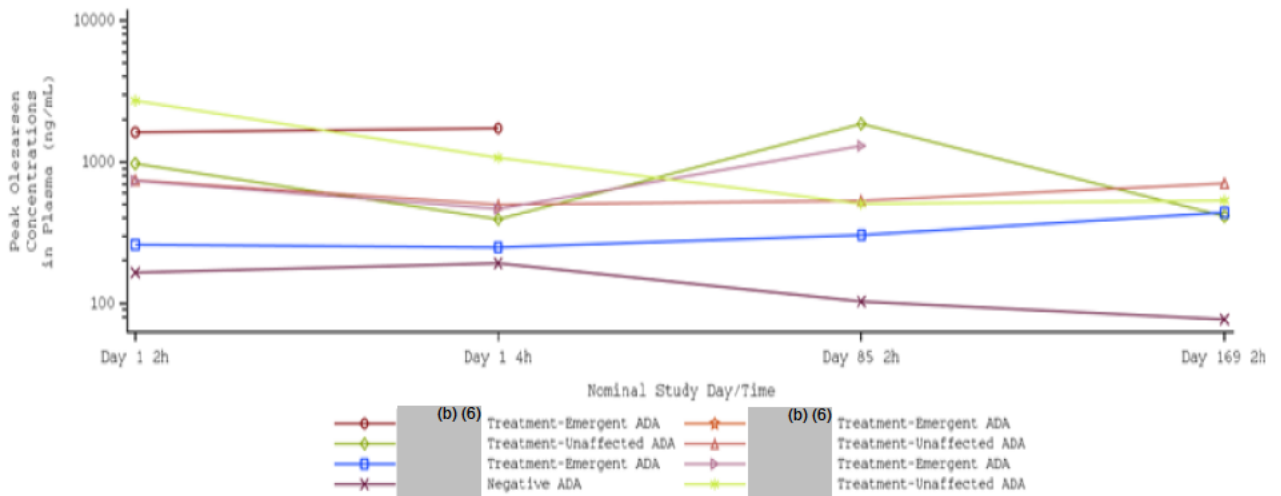
Day	1	29	57	85	113	141	169	197	253	309
Negative ADA	7	8	7	7	8	7	8	7	7	8
Treatment-Unaffected ADA	3	3	3	3	2	2	2	2	1	2
Treatment-Emergent ADA	10	9	8	9	9	9	9	8	8	7

Source: Figure 14.2.5.1.4.1 of 678354-CS3-study-report
 Abbreviations: ADA, antidrug antibodies; SEM, standard error of the mean; Q4W, every four weeks

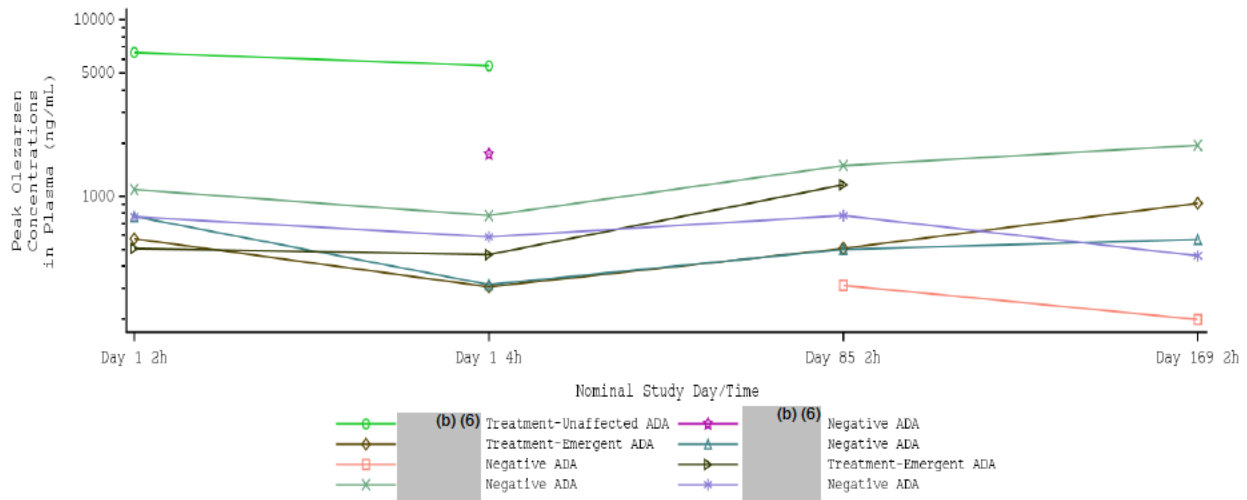
Peak plasma olezarsen concentrations in the two patients with high peak ADA titers in Trial ISIS 678354-CS3 were generally in agreement with other patients in their respective treatment groups, regardless of subject ADA category or peak ADA titer levels (Figure 52). Therefore, high ADA titer does not appear to impact peak plasma concentrations.

Figure 52. Representative Individual Patient Plasma Peak Olezarsen Concentration (ng/mL) Over Time With Semi-Log Scale, Trial ISIS 678354-CS3

Olezarsen 50 mg Q4W



Olezarsen 80 mg Q4W



Source: Figure 14.2.5.1.8 of 678354-CS3-study-report.

Note: Plasma peak concentrations in patients with peak ADA titer of 25600 (Patient (b) (6), red circle, top panel and Patient (b) (6), black triangle, bottom panel)

Abbreviations: ADA, antidrug antibodies; Q4W, every four weeks; SEM, standard error of the mean

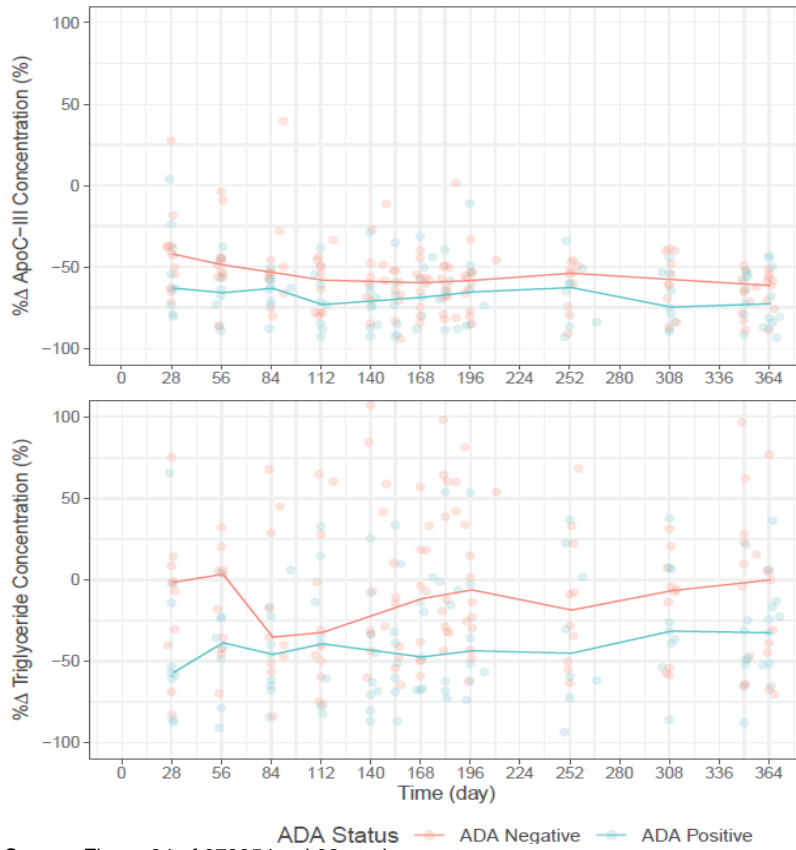
In conclusion, C_{max} was unaltered, while higher C_{trough} was observed in ADA-positive patients.

Impact of Immunogenicity on Pharmacodynamics and Efficacy

Since the molecular target of olezarsen is human *apoC-III* mRNA, plasma ApoC-III level is the direct biomarker of olezarsen PD effect, and therefore, the impact of immunogenicity on plasma ApoC-III reductions over time was evaluated across clinical studies. The presence of anti-olezarsen antibodies did not have any effect on ApoC-III reduction in olezarsen-treated patients with HTG/sHTG or patients with FCS across olezarsen clinical studies. In the pivotal trial in patients with FCS (ISIS 678354-CS3), the mean percent change in ApoC-III over time by subject ADA category following 80 mg (the proposed dose) olezarsen administered Q4W for 52 weeks does not reveal a consistent difference in ApoC-III reduction between ADA-negative patients and ADA-positive patients (Figure 54). A similar result is observed when examining the mean ($\pm$ SEM) percent change in TG over time, though the variability in the data is greater as TG was highly influenced by other factors such as diet. However, the available data is limited to make definitive conclusions.

Figure 53. Percent Change From Baseline-Time Profiles by ADA Status – Olezarsen 50 mg Q4W, Trial CS3

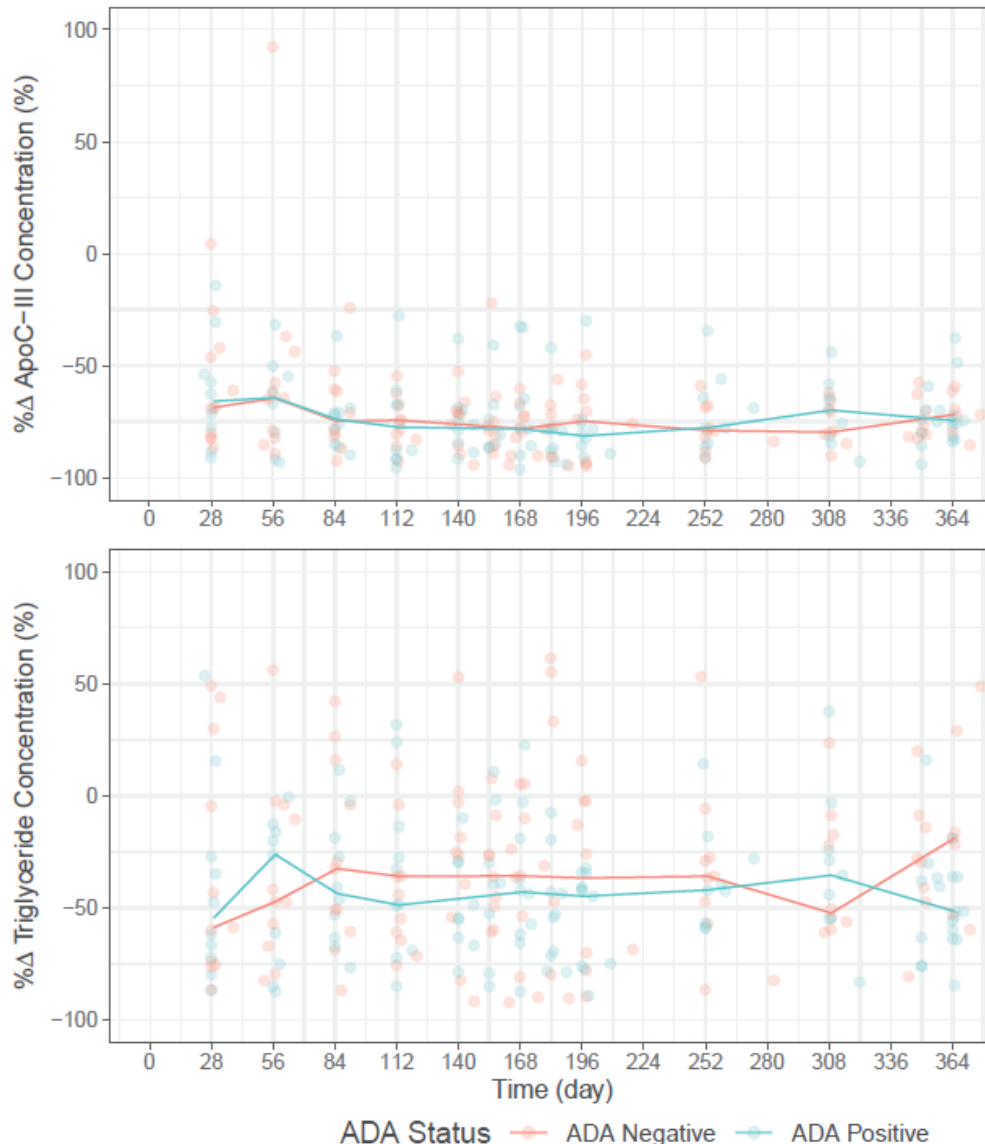
Olezarsen 50 mg Q4W



Source: Figure 24 of 678354-ppk02-study-report
Top Panel: apoC-III. Bottom Panel: TG.
Abbreviations: ADA, antidrug antibodies; apo, apolipoprotein; Q4W, every four weeks; TG, triglycerides

Figure 54. Percent Change From Baseline-Time Profiles by ADA Status – Olezarsen 80 mg Q4W, Trial CS3

Olezarsen 80 mg Q4W



Source: Figure 25 of 678354-ppk02-study-report
Top Panel: apoC-III. Bottom Panel: TG.
Abbreviations: ADA, antidrug antibodies; apo, apolipoprotein; Q4W, every four weeks; TG, triglycerides

Impact of Immunogenicity on Safety

In Trial ISIS 678354-CS3, there does not appear to be any association of patient ADA status (negative, treatment-unaffected, or treatment-emergent) with the frequency of TEAEs, their severity, or their relationship to treatment, nor are there any such trends for serious TEAEs.

For other adverse events of interest (OAEIs), there was no apparent correlation between ISRs, bleeding, thrombocytopenia, renal, or hepatic TEAEs and ADA status. With respect to hypersensitivity OAEIs, there was no obvious relationship between hypersensitivity reactions

and ADA status, though small sample sizes limit interpretation of the data. For more details, please refer to Section [7.7.8](#).

14.5. Pharmacometrics Assessment

The population PK, exposure-ApoC-III, and exposure-TG modeling was considered reasonable for describing olezarsen, ApoC-III, and TG concentrations following a single or multiple dose administration of olezarsen and for performing PK and PD simulations to predict steady-state olezarsen exposure metrics and the effect on ApoC-III and TG levels. The PK and PD modelling were utilized to support the current submission as outlined below.

Table 116. Utility of the Population PK Modeling

Utility of the Final Model	Reviewer's Comments
- The PK model included weight as a covariate on CL/F, Vc/F, Q/F, Vp/F, and k_a. Japanese participants had 29% higher Vc/F. Both k_a and relative F were higher for the autoinjector compared to the vial by 13% and 5%, respectively. ADA positive status with ADA titer of 100 was associated with 30% decrease in CL/F. - The model-predicted PK was used to develop 2 independent exposure-response models, describing the relationship between olezarsen concentrations and either apoC-III or triglyceride (TG) concentrations. - The exposure-apoC-III model estimated an IC_{50} (concentration at half maximum inhibition effect on apoC-III production rate) of 0.44 ng/mL, in patients with FCS. The Applicant's model estimated a 30% increase in IC_{50} in ADA positive subjects with an ADA titer of 50. The exposure-TG model estimated an EC_{50} (concentration at half maximum effect on TG elimination rate constant) of 1.48 ng/mL, in patients with FCS. The Applicant's model estimated an increase in EC_{50} with an ADA titer above 50. - The PK and exposure-response models were used to perform population simulations for olezarsen 50 mg or 80 mg, administered every 28 days (Q4W) or 30 days (Q1M), to support dose selection in patients with FCS. The Applicant's simulations indicated that the PK, apoC-III, and TG profiles for Q4W and Q1M dosing overlap following first dose and at steady-state with only marginal difference in median olezarsen concentrations, percentage change from baseline in apoC-III and TG for the respective doses and dosing regimens.	- The PK model was considered reasonable in predicting median and individual observed concentrations of olezarsen and their variability in healthy volunteers, patients with FCS and patients with HTG and CVD. - ADA titer was found to be the most influential covariate on AUC and C_{trough}. ADA titer did not affect C_{max}. About 97% of subjects and PK samples collected had ADA titer below or equal to 3200, which was estimated to result in 194% and 400% increase in median steady-state AUC (AUC_{ss}) and C_{trough} ($C_{trough,ss}$), compared to ADA negative subjects. At the mean ADA titer of 800, median AUC_{ss} and $C_{trough,ss}$ are predicted to increase by 120% and 250% compared to ADA negative subjects. Although ADA titers are expected to increase $C_{trough,ss}$ and AUC_{ss}, the estimated $C_{trough,ss}$ remain well below $C_{max,ss}$. - The Applicant's exposure-apoC-III and exposure-TG models are acceptable and adequately describes the median and individual observed apoC-III and TG concentrations and their variability in healthy volunteers, patients with FCS and patients with HTG and CVD. - The Applicant did not provide the rationale and physiological explanation for including ADA status and titer on IC_{50}. The effect of ADA status/titer could be confounded by another unexplored covariate and looks driven only by study ISIS 678354-CS3 in FCS patients. The model without ADA status and titer effect did not affect the PD model parameters, except for the effect of FCS disease on IC_{50}, suggesting that FCS patients are estimated to IC_{50} of 0.63 ng/mL).

Utility of the Final Model	Reviewer's Comments
The Applicant performed exploratory analysis to evaluate the relationship between the change from baseline (CFB) in platelet count versus cumulative AUC (cAUC) and C_{max} in studies ISIS 678354-CS3 and -CS8, concluding that there were no substantial trends in the observed change from baseline or the maximum decrease from baseline in platelet count across the entire range of cumulative AUC or C_{max}.	- The proposed doses of 80 mg olezarsen administered Q4W or Q1M are acceptable and estimated to achieve, at the end of the dosing interval (at $C_{trough,ss}$), a percent reduction from baseline in apoC-III of 74% for Q4W or 71% for Q1M, and percent reductions from baseline in TG of 32% for Q4W and 30% for Q1M, in patients with FCS. - The reviewer's assessment of the relationship between olezarsen exposure metrics and the maximum reduction in platelet count is relatively shallow, with most patients experiencing less than grade 1 thrombocytopenia, and most patients with highest maximum decrease in platelets counts having no ADA or maximum ADA titer lower or equal 800. Similar pattern was observed for percent maximum decrease from baseline in platelets counts and exposure-metrics.

Source: FDA reviewer

Abbreviations: ADA, antidrug antibody; apo, apolipoprotein; AUC, area under the concentration-time curve; cAUC, cumulative area under the concentration-time curve; CFB, change from baseline; CL/F, apparent clearance; C_{max} , maximum plasma concentration; C_{trough} , trough plasma concentration; CVD, cardiovascular disease; EC_{50} , half maximal effective concentration; F, bioavailability; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; IC_{50} , half maximal inhibitory concentration; k_a , absorption rate constant; PD, pharmacodynamics; PK, pharmacokinetics; Q/F, apparent intercompartmental clearance; Q1M, every 30 days; Q4W, every four weeks; TG, triglycerides; V_d/F , apparent central volume; V_p/F , apparent peripheral volume

14.5.1. Applicant's PK Analysis

The Applicant developed a population PK model for olezarsen to characterize the PK properties of olezarsen administered SC. The data for PK modeling were collected from three Phase 1 studies in healthy subjects (ISIS 678354-CS1, ISIS 678354-CS20, and AKCEA-CS1), one Phase 2 study (ISIS 678354-CS2) in patients with HTG and established CVD or at high risk for CVD, and two Phase 3 studies (ISIS 678354-CS3 and -CS8) in patients with FCS and in patients with CVD and HTG, respectively ([Table 117](#)).

The PK dataset consisted of 6535 quantifiable PK samples from 415 subjects. Concentrations below the limit of quantification (n=419, <0.13 ng/mL) were excluded from the analysis dataset as they represented 6% (less than 10%) of all the data.

[Table 118](#) summarizes the demographic characteristics of subjects included in the PK analyses, stratified by study. [Table 119](#) summarizes the ADA titers by study. Most patients (85%, n=122) had ADA titers between 50 and 800, 12% of patients (n=17) had ADA titers between 1600 and 3200, 3.4% of patients (n=5) had ADA titers between 6400 and 25600, among whom one patient had a single transient peak ADA at 51200.

Table 117. Studies Included in the Population PK Analysis

Study	Study Description	Dose (mg)	N*	PK Sampling
ISIS 678354-CS1	Phase 1, double-blind, placebo-controlled, dose escalation study in HV	10, 30, 60, 90, 120 mg SD or placebo 15, 30 mg QW or placebo 60 mg Q4W or placebo	67	Single dose D1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h. D2: 24 h. D3 48 h. D8, D15, D30, D60, D90, D120, D150: anytime. QW dose D1, D36: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h. D2, D37: 24 h. D3, D38: 48 h. D43, D64, D92, D127, D155, D183: anytime. Q4W dose D1, D85: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h. D2, D86: 24 h. D3, D87: 48 h. D8, D15, D43, D71, D92, D99, D113, D127, D141, D176, D204, D232: anytime.
AKCEA-CS1 †	Phase 1, randomized, double blind, placebo-controlled, single ascending and multiple dose study in Japanese HV conducted in the United States	20, 30, 40, 60, 80, 90 mg SD 60, 80 mg Q4W	28	30, 60, 90 mg SD D1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h. D2: 24 h. D3, D8, D15, D30, D60, D90, D120, D150: pre-dose. 60 mg Q4W D1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h. D2: 24 h. D3: 48 h. D8, D15, D29: pre-dose. D43, D57: pre-dose. D71, D85: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h. D86: 24 h. D87: 48 h. D92, D99, D113, D127, D141, D176, D204: pre-dose.
ISIS 678354-CS20	Phase 1, single-dose, randomized, open-label, two-period crossover, bioequivalence study comparing two drug presentations vial and autoinjector in HV	50 mg (vial and autoinjector); 80 mg (vial and autoinjector)	104	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4.5, 6, 8, 10, 12, 16, 24, 36, 48, 96, 168 h for each period.

SC = subcutaneous, D = Day, SD = single dose, QW = once every week, Q2W = once every 2 weeks, Q4W = once every 4 weeks.

* Total number of subjects (active + placebo). For ISIS 678354-CS1, 49 active and 18 placebo; for AKCEA-CS1, 22 active and 6 placebo.

† Only data for ISIS 678354 included.

NDA 218614
Tryngolza (olezarsen sodium)

(Table 117 continued)

Study	Study Description	Dose (mg)	N*	PK Sampling
ISIS 678354-CS2	Phase 2, randomized, double-blind, dose-ranging, placebo-controlled study in patients with HTG and CVD	10 mg QW or placebo 15 mg Q2W or placebo 10, 50 mg Q4W or placebo	114	QW and Q2W dose D1, D169: pre-dose for all patients and pre-dose 1, 2, 4, 8 h for patients in PK subgroup only. D2, D170: 24 h for patients in PK subgroup only. D29, D57, D85, D113, D141: pre-dose. D171: 48 h for patients in PK subgroup only. D176, D183, D197, D253, D365: pre-dose. Q4W dose D1, D141: pre-dose for all patients and pre-dose 1, 2, 4, 8 h for patients in PK subgroup only. D2, D142: 24 h for patients in PK subgroup only. D29, D57, D85, D113: pre-dose. D143: 48 h for patients in PK subgroup only. D148, D155, D169, D197, D253, D365: pre-dose.
ISIS 678354-CS3	Phase 3, randomized, double-blind, placebo-controlled study in patients with FCS	50, 80 mg Q4W or placebo	66	All patients D1: pre-dose, 2, 4 h. D15: anytime. D85, D169: pre-dose, 2 h. D29, D57, D113, D141, D197, D253, D309: pre-dose. D365: anytime.
ISIS 678354-CS8	Phase 2b, randomized, double-blind, placebo-controlled study in patients with HTG and CVD	50, 80 mg Q4W or placebo	154	All patients D1, D29, D85, D169, D253: pre-dose. D365: any-time.

HTG = hypertriglyceridemia, CVD = cardiovascular disease, FCS = familial chylomicronemia syndrome.

SC = subcutaneous, D = Day, SD = single dose, QW = once every week, Q2W = once every 2 weeks, Q4W = once every 4 weeks.

Source: Applicant's Population PK/PD Report (678354-ppk02-study-report), Table 1, page45.

Abbreviations: PK, pharmacokinetics

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Table 118. Summary of Demographic Characteristics, Stratified by Study

	678354-CS1 (N=49)	678354-CS20 (N=104)	AKCEA-CS1 (N=22)	678354-CS2 (N=82)	678354-CS3 (N=43)	678354-CS8 (N=115)	Overall (N=415)
Age (years)							
Mean (SD)	50.8 (10.3)	44.5 (11.9)	41.7 (11.3)	65.8 (8.05)	45.5 (12.8)	61.3 (10.5)	54.1 (14.0)
Median [Min, Max]	51.0 [21.0, 64.0]	46.0 [19.0, 64.0]	40.5 [21.0, 58.0]	67.0 [46.0, 80.0]	45.0 [18.0, 78.0]	62.0 [35.0, 83.0]	55.0 [18.0, 83.0]
Baseline weight (Kg)							
Mean (SD)	86.9 (15.8)	80.0 (12.2)	66.1 (9.19)	93.5 (14.6)	64.9 (14.7)	97.0 (23.3)	85.9 (20.1)
Median [Min, Max]	88.8 [56.3, 122]	81.0 [49.2, 110]	69.0 [51.3, 82.6]	92.3 [60.3, 131]	63.7 [35.8, 113]	95.3 [58.2, 196]	85.3 [35.8, 196]
eGFR (mL/min/1.73m²)							
Mean (SD)	96.3 (13.9)	105 (17.9)	102 (10.5)	80.7 (15.3)	109 (19.7)	86.1 (21.6)	94.3 (20.8)
Median [Min, Max]	96.8 [52.2, 120]	104 [68.2, 155]	103 [80.5, 118]	80.2 [53.0, 111]	113 [53.5, 145]	91.0 [27.1, 132]	95.5 [27.1, 155]
ALT (U/L)							
Mean (SD)	21.7 (9.92)	19.4 (8.16)	22.5 (12.2)	24.2 (9.75)	21.3 (14.9)	26.8 (16.4)	23.0 (12.6)
Median [Min, Max]	18.0 [4.00, 46.0]	17.0 [5.00, 48.0]	20.0 [7.00, 55.0]	23.5 [9.00, 50.0]	15.0 [6.00, 59.0]	23.0 [9.00, 90.0]	20.0 [4.00, 90.0]
AST (U/L)							
Mean (SD)	17.4 (3.76)	17.2 (4.62)	18.3 (5.54)	20.2 (7.62)	22.9 (10.7)	21.3 (11.4)	19.6 (8.45)
Median [Min, Max]	17.0 [10.0, 26.0]	16.0 [8.00, 35.0]	16.5 [11.0, 32.0]	19.0 [10.0, 51.0]	20.0 [9.00, 54.0]	18.0 [10.0, 77.0]	17.0 [8.00, 77.0]
Bilirubin (mg/dL)							
Mean (SD)	0.610 (0.221)	0.552 (0.192)	0.764 (0.316)	0.526 (0.208)	0.685 (0.305)	0.500 (0.201)	0.564 (0.233)
Median [Min, Max]	0.550 [0.230, 1.26]	0.530 [0.170, 1.14]	0.700 [0.400, 1.60]	0.470 [0.210, 1.16]	0.600 [0.140, 1.66]	0.470 [0.190, 1.41]	0.520 [0.140, 1.66]
Albumine (g/L)							
Mean (SD)	43.1 (2.84)	42.8 (3.01)	43.9 (3.54)	43.4 (2.18)	45.8 (2.86)	43.1 (3.08)	43.4 (2.99)
Median [Min, Max]	42.0 [39.0, 50.0]	42.0 [37.0, 52.0]	43.0 [36.0, 49.0]	43.0 [37.0, 48.0]	45.0 [40.0, 52.0]	43.0 [32.0, 54.0]	43.0 [32.0, 54.0]
Baseline ApoC-III (mg/dL)							
Mean (SD)	12.1 (4.42)	8.50 (3.11)	14.2 (5.52)	16.3 (4.85)	27.6 (11.3)	15.9 (7.26)	14.8 (8.18)
Median [Min, Max]	11.0 [5.00, 28.0]	7.94 [2.82, 18.3]	12.1 [8.90, 24.8]	15.5 [7.79, 34.0]	26.5 [10.4, 57.2]	14.2 [6.73, 61.1]	13.3 [2.82, 61.1]
Baseline Triglyceride (mg/dL)							
Mean (SD)	199 (124)	99.7 (50.7)	154 (89.1)	278 (110)	2560 (1460)	300 (243)	460 (870)
Median [Min, Max]	157 [78.0, 806]	83.0 [35.0, 275]	129 [54.0, 358]	253 [117, 687]	2110 [768, 7530]	232 [102, 1650]	205 [35.0, 7530]

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(Table 118 continued)

	678354-CS1 (N=49)	678354-CS20 (N=104)	AKCEA-CS1 (N=22)	678354-CS2 (N=82)	678354-CS3 (N=43)	678354-CS8 (N=115)	Overall (N=415)
Drug presentation							
Vial	49 (100%)	52 (50.0%)	22 (100%)	82 (100%)	43 (100%)	115 (100%)	363 (87.5%)
Autoinjector	0 (0%)	52 (50.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	52 (12.5%)
Sex							
Male	34 (69.4%)	75 (72.1%)	15 (68.2%)	61 (74.4%)	17 (39.5%)	74 (64.3%)	276 (66.5%)
Female	15 (30.6%)	29 (27.9%)	7 (31.8%)	21 (25.6%)	26 (60.5%)	41 (35.7%)	139 (33.5%)
Race							
White	34 (69.4%)	49 (47.1%)	0 (0%)	78 (95.1%)	34 (79.1%)	106 (92.2%)	301 (72.5%)
Black or AA	5 (10.2%)	53 (51.0%)	0 (0%)	2 (2.4%)	0 (0%)	8 (7.0%)	68 (16.4%)
Asian (not Japanese)	8 (16.3%)	0 (0%)	0 (0%)	0 (0%)	6 (14.0%)	1 (0.9%)	15 (3.6%)
Japanese	0 (0%)	0 (0%)	22 (100%)	0 (0%)	0 (0%)	0 (0%)	22 (5.3%)
AIAN	2 (4.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.5%)
NHOPI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.3%)	0 (0%)	1 (0.2%)
Other/Unknown	0 (0%)	2 (1.9%)	0 (0%)	2 (2.4%)	2 (4.7%)	0 (0%)	6 (1.4%)
Region							
US	0 (0%)	104 (100%)	22 (100%)	51 (62.2%)	12 (27.9%)	111 (96.5%)	300 (72.3%)
Japan	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rest of World	49 (100%)	0 (0%)	0 (0%)	31 (37.8%)	31 (72.1%)	4 (3.5%)	115 (27.7%)
Disease Status							
Healthy	49 (100%)	104 (100%)	22 (100%)	0 (0%)	0 (0%)	0 (0%)	175 (42.2%)
Patient with HTG and CVD	0 (0%)	0 (0%)	0 (0%)	82 (100%)	0 (0%)	115 (100%)	197 (47.5%)
Patient with FCS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	43 (100%)	0 (0%)	43 (10.4%)
Patient unrecorded info	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

(Table 118 continued)

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	678354-CS1 (N=49)	678354-CS20 (N=104)	AKCEA-CS1 (N=22)	678354-CS2 (N=82)	678354-CS3 (N=43)	678354-CS8 (N=115)	Overall (N=415)
Hepatic Impairment							
Normal	47 (95.9%)	104 (100%)	20 (90.9%)	75 (91.5%)	38 (88.4%)	107 (93.0%)	391 (94.2%)
Mild	2 (4.1%)	0 (0%)	1 (4.5%)	7 (8.5%)	5 (11.6%)	8 (7.0%)	23 (5.5%)
Moderate	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Liver Transplant	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal Impairment							
Normal	33 (67.3%)	86 (82.7%)	18 (81.8%)	27 (32.9%)	34 (79.1%)	61 (53.0%)	259 (62.4%)
Mild	15 (30.6%)	18 (17.3%)	4 (18.2%)	48 (58.5%)	8 (18.6%)	38 (33.0%)	131 (31.6%)
Mild to Moderate	1 (2.0%)	0 (0%)	0 (0%)	7 (8.5%)	1 (2.3%)	11 (9.6%)	20 (4.8%)
Moderate to Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (3.5%)	4 (1.0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	1 (0.2%)
ESRD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ADA positive at baseline							
Negative	0 (0%)	0 (0%)	0 (0%)	1 (1.2%)	7 (16.3%)	8 (7.0%)	16 (3.9%)
Positive	0 (0%)	0 (0%)	1 (4.5%)	3 (3.7%)	14 (32.6%)	20 (17.4%)	38 (9.2%)
Unknown	49 (100%)	104 (100%)	21 (95.5%)	78 (95.1%)	22 (51.2%)	87 (75.7%)	361 (87.0%)
ADA positive (any time)							
Negative	0 (0%)	0 (0%)	16 (72.7%)	60 (73.2%)	16 (37.2%)	57 (49.6%)	149 (35.9%)
Positive	0 (0%)	0 (0%)	6 (27.3%)	22 (26.8%)	27 (62.8%)	58 (50.4%)	113 (27.2%)
Unknown	49 (100%)	104 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	153 (36.9%)

Source: FDA reviewer.

Abbreviations: AA, African American; ADA, antidrug antibody; AIAN, American Indian or Alaska Native; ALT, alanine aminotransferase; apo, apolipoprotein; AST, aspartate aminotransferase; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; max, maximum; min, minimum; SD, standard deviation; US, United States

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Table 119. Summary of ADA Titers, Stratified by Study and ADA Titer Groups

	AKCEA-CS1 (N=61)	678354-CS2 (N=140)	678354-CS3 (N=249)	678354-CS8 (N=256)	Overall (N=706)
ADA titer					
Mean (SD)	110 (78.4)	324 (699)	1330 (4030)	921 (4490)	876 (3640)
Median [Min, Max]	50.0 [50.0, 400]	50.0 [50.0, 3200]	100 [50.0, 25600]	100 [50.0, 51200]	100 [50.0, 51200]
Observations per ADA titer group					
50 - 200	60 (98.4%)	118 (84.3%)	147 (59.0%)	186 (72.7%)	511 (72.4%)
400 - 800	1 (1.6%)	10 (7.1%)	61 (24.5%)	48 (18.8%)	120 (17.0%)
1600 - 3200	0 (0%)	12 (8.6%)	26 (10.4%)	17 (6.6%)	55 (7.8%)
6400 - 25600	0 (0%)	0 (0%)	15 (6.0%)	4 (1.6%)	19 (2.7%)
51,200	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.1%)

Source: FDA reviewer

Abbreviations: ADA, antidrug antibody; max, maximum; min, minimum; SD, standard deviation

Final Population PK Model

The PK model for olezarsen consisted of a two-compartment disposition model with first-order absorption and a linear elimination from the central compartment. Between subject variability (BSV) terms were included on apparent clearance (CL/F), apparent central volume (Vc/F), apparent inter-compartmental clearance (Q/F), apparent peripheral volume (Vp/F), and the absorption rate (k_a). Between-occasion variability was included on CL/F and Vp/F, where occasion is the time-varying ADA positivity status (binary variable, with ADA positive status defined from time of first ADA appearance). The proportional residual unexplained variability (RUV) was implemented as an additive residual error on the log-scale. The parameter estimates from the final octreotide PK model are listed in [Table 120](#).

Weight was included as a covariate on CL/F, Vc/F, Q/F, Vp/F, and k_a . Japanese participants (i.e., Trial AKCEA-CS1) had 29% higher Vc/F compared to the other ethnicities across the studies. Both k_a and relative F were higher for the autoinjector compared to the vial by 13% and 5%, respectively. ADA-positive status with ADA titer of 100 was associated with 30% decrease in CL/F.

The goodness of fit (GOF) plots from the final PK model are shown in [Figure 55](#) and the prediction-corrected visual predict check (pcVPC) plots are shown in [Figure 56](#).

Reviewer Comment and Assessment of the Population PK Model

Overall, the Applicant's PK model is acceptable and adequately describes the individual observed concentrations of olezarsen and their variability in healthy volunteers, patients with FCS and patients with HTG and CVD.

- The PK parameters from the PK model were estimated with an acceptable precision (<23% relative standard error [RSE]). The estimated interindividual random error (η -) shrinkage was low (<30%) and acceptable for the reliable graphical assessment of covariate effects, except for k_a (η -shrinkage =55%). The residual error (ϵ -) shrinkage was low (9%), indicating the informativeness of the GOF plots to diagnose structural and residual error model misspecifications. The GOF plots show that the PK model fitted the observed data well with no critical trends or bias in the predicted versus the observed concentrations of olezarsen and in the conditional weighted residuals (CWRES) versus predictions or time from all studies and olezarsen dose levels.
- The pcVPC plots, stratified by ADA status, indicate that the Applicant's PK model reasonably captures and describes the observed median olezarsen concentrations and their variability from all studies with minimal bias.
- ADA titer was found to be the most influential covariate on CL/F, AUC and C_{trough} . [Figure 57](#) summarizes the predicted effect of ADA titer on the steady-state exposure metrics (AUC_{ss} , $C_{\text{max,ss}}$ and $C_{\text{trough,ss}}$).

Table 120. Parameter Estimates of the Final Olezarsen PK Model

Parameter Name	Estimated Value (%RSE)
Apparent Clearance (CL/F, L/h) [†]	13.7 (3.7)
Covariate of Weight on CL/F	0.961 (12.4)
Covariate of ADA (binary) on CL/F	0.697 (5.6)
Covariate of ADA Titer (continuous) on CL/F	-0.208 (19.8)
Apparent Central Volume of Distribution (V _c /F, L) ^{††}	96.3 (5.3)
Covariate of Weight on V _c /F	2.23 (9.4)
Covariate of Race (Japanese) on V _c /F	1.29 (7.2)
Apparent Inter-compartmental Clearance (Q/F, L/h) [#]	4.15 (6.1)
Covariate of Weight on Q/F	1.47 (16.8)
Apparent Peripheral Volume of Distribution (V _p /F, L) ^{###}	3860 (8.5)
Covariate of Weight on V _p /F	1.42 (23.4)
Covariate of ADA Titer (continuous) on V _p /F	-0.241 (14.2)
First Order Absorption Rate Constant (k _a , 1/h) [*]	1.17 (4.0)
Covariate of Weight on k _a	0.857 (20.8)
Covariate of Drug Presentation on k _a	1.13 (4.3)
Covariate of Drug Presentation on Relative Bioavailability (F) ^{**}	1.05 (1.3)
Between Subject Variability for CL/F (%)	43.2 (11.2)
Correlation between CL/F-V _c /F (-)	0.899 (8.3)
Between Subject Variability for V _c /F (%)	68.2 (6.0)
Correlation between CL/F-Q/F (-)	0.629 (11.0)
Correlation between V _c /F-Q/F (-)	0.83 (6.4)
Between Subject Variability for Q/F (%)	83.7 (5.3)
Correlation between CL/F-V _p /F (-)	0.416 (14.1)
Correlation between V _c -V _p /F (-)	0.672 (7.3)
Correlation between Q/F-V _p /F (-)	0.965 (5.0)
Between Subject Variability for V _p /F (%)	115 (4.8)
Between Subject Variability for K _a (%)	29.9 (11.1)
Between Occasion Variability for CL/F by ADA Status (%)	33 (7.8)
Between Occasion Variability for V _p /F by ADA Status (%)	29.6 (12.0)
Residual Unexplained Variability (Proportional) (%) [§]	31.6 (1.0)

ADATITER = ADA Titer, CV = coefficient of variation, RSE = relative standard error.

[†]CL/F = 13.7 · (WT/70)^{0.961} · 0.697 (if ADA is positive) · (ADATITER/100)^{-0.208} (if ADATITER > 0)

^{††}V_c/F = 96.3 · (WT/70)^{2.23} · 1.29 (for Japanese [AKCEA-CS1])

[#]Q/F = 4.15 · (WT/70)^{1.47}

^{###}V_p/F = 3860 · (WT/70)^{1.42} · (ADATITER/100)^{-0.241} (if ADATITER > 0)

^{*}k_a = 1.17 · (WT/70)^{0.857} · 1.13 (if autoinjector as drug presentation)

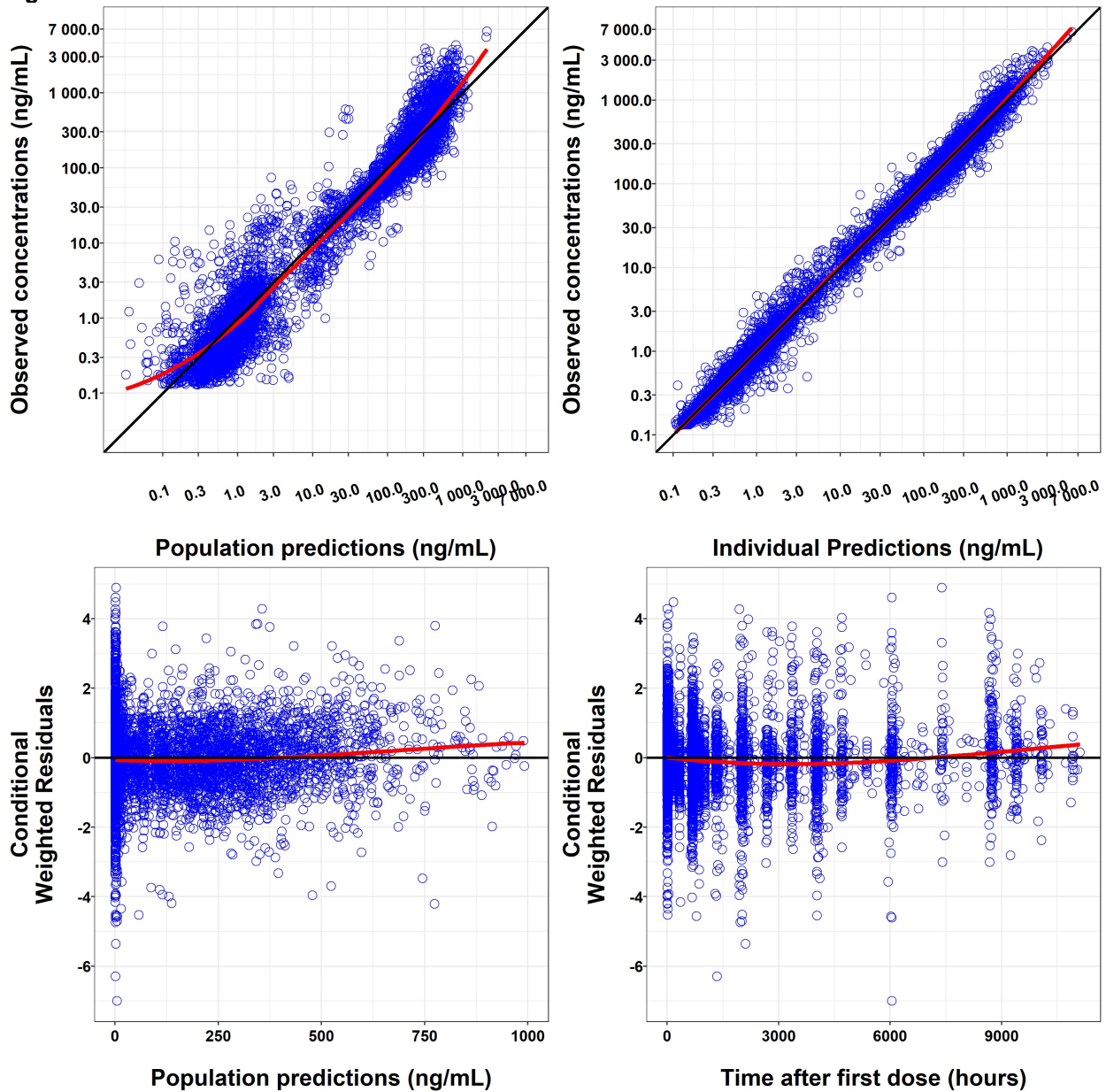
^{**}F = 1 · 1.05 (if autoinjector as drug presentation)

[§] Additive on natural log scale.

Source: Applicant's Response to Information Request (September 5, 2024), Table 2, page 9.

Abbreviations: ADA, antidrug antibody; CL/F, apparent clearance; F, relative bioavailability; k_a, absorption rate constant; PK, pharmacokinetics; Q/F, apparent intercompartmental clearance; V_c/F, apparent central volume; V_p/F, apparent peripheral volume

Figure 55. Goodness of Fit Plots From the Final PK Model



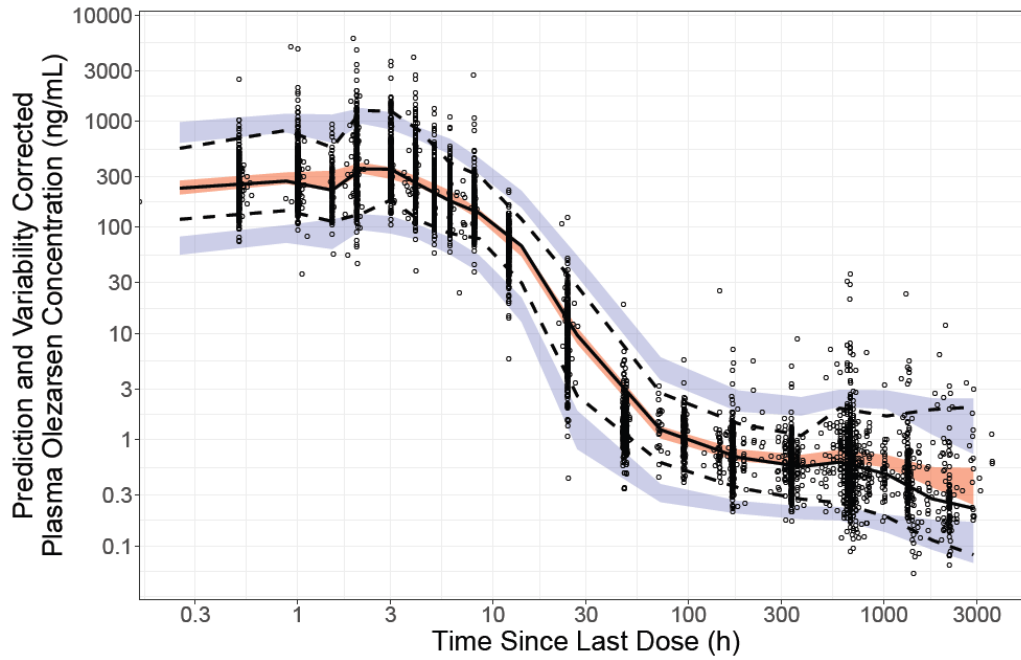
Source: FDA reviewer

Note: log₁₀-log₁₀ scale is used for the observed versus predicted concentrations; CWRES=conditional weighted residuals; red lines represent loess smooth curves, and the black lines represent the line of unity $y = x$ or $y = 0$.

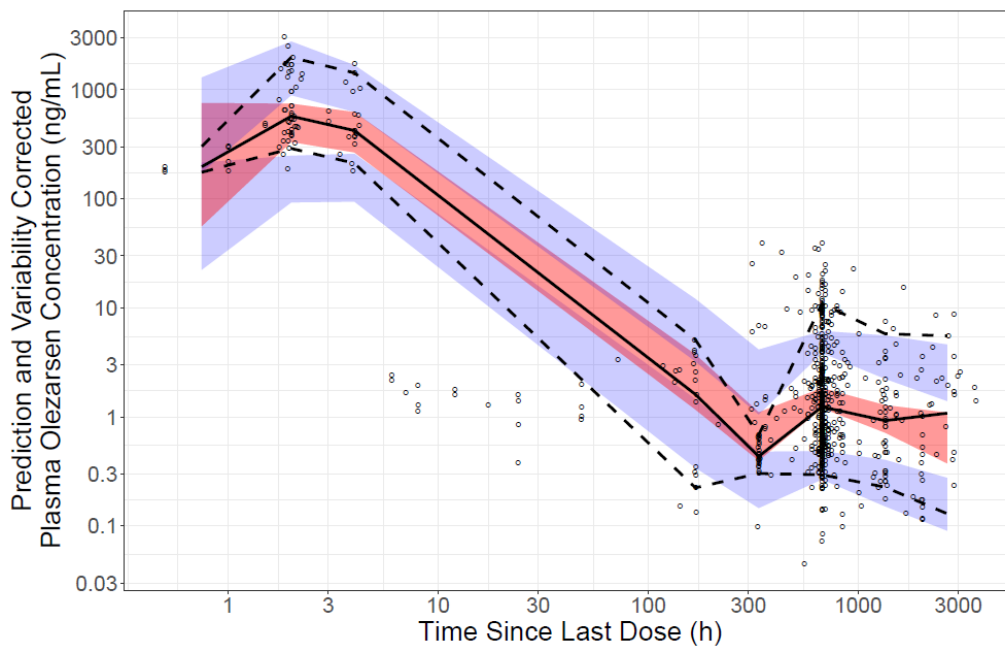
Abbreviations: PK, pharmacokinetics

Figure 56. Prediction-Corrected Visual Predictive Check From Final PK Model, by ADA Status

A. ADA negative status



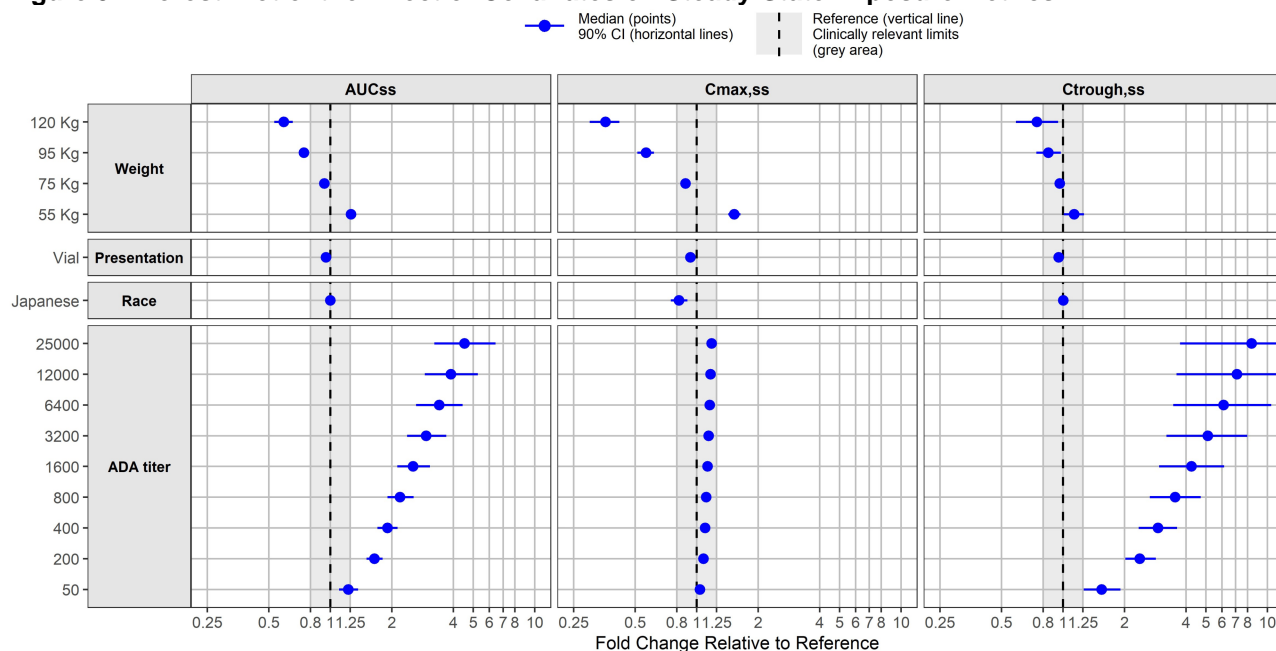
B. ADA positive status:



Source: Applicant's Response to Information Request (September 5, 2024), Figures 1 and 2, pages 5 to 6
Note: Data are presented on log-logarithmic scale. Open circles: individual concentrations, dashed lines: 5th and 95th percentiles of observed data, solid line: observed median concentrations, and shaded area: 95% confidence interval around the model predicted 5th, 50th, and 95th percentiles.

Abbreviations: ADA, antidrug antibody; PK, pharmacokinetics;

Figure 57. Forest Plot of the Effect of Covariates on Steady-State Exposure Metrics



Source: FDA reviewer

Note: The reference subject is a 70 kg, non-Japanese, ADA negative subject, using the autoinjector to administer olezarsen. Dots and error bars represent the median of the predicted fold change from the reference subject and its associated 90% CI for each covariate evaluated in a univariate manner; these values are calculated based on 1000 sampled PK parameter vectors from the variance-covariance matrix of the final PK model. The reference area indicates the 80%-125% margins relative to the reference subject.

Abbreviations: ADA, antidrug antibody; AUC_{ss}, area under the concentration-time curve at steady state; CI, confidence interval; C_{max,ss}, maximum plasma concentration at steady state; C_{trough,ss}, trough plasma concentration at steady state; PK, pharmacokinetics;

About 97% of subjects and PK samples collected had ADA titer below or equal to 3200, which was estimated to result in 194% and 400% increase in median AUC_{ss} and C_{trough,ss}, compared to ADA-negative subjects, respectively. At the mean ADA titer of 800, median AUC_{ss} and C_{trough,ss} are predicted to increase by 120% and 250% compared to ADA-negative subjects. Although ADA titers are expected to increase C_{trough,ss} and AUC_{ss}, the estimated C_{trough,ss} are expected to remain well below C_{max,ss}, which are not affected by ADA titer effect.

14.5.2. Applicant's Exposure-Response Analyses

The Applicant used the model-predicted PK to develop two exposure-response models, using sequential PK-PD modeling. The exposure-response models described the relationship between olezarsen concentrations and either ApoC-III concentrations or TG concentrations.

The exposure-ApoC-III dataset consisted of 4518 quantifiable ApoC-III concentrations paired with PK information from 415 subjects. ApoC-III concentrations below the limit of quantification (n=196, <0.94 mg/dL) were excluded from the analysis dataset as they represented less than 10% of all the data. The exposure-TG dataset consisted of 4728 TG concentrations paired with PK information from 415 subjects. No trends in ApoC-III or TG levels over time were observed for placebo subjects, hence, placebo subjects were excluded from the analyses.

14.5.2.1. Exposure-ApoC-III Model

The exposure-ApoC-III model consisted of an indirect response model with an inhibitory drug effect on ApoC-III production rate (K_{in}). The drug effect on K_{in} was described as an inhibitory E_{max} function with maximum inhibition (I_{max}) and a concentration at half maximum inhibition (IC_{50}). BSV terms were included on the ApoC-III removal rate constant (K_{out}) and IC_{50} parameters. The RUV in ApoC-III concentrations was implemented using a proportional residual error model, with separate RUV estimated by ADA status.

[Table 121](#) summarizes the parameter estimates of the final exposure-ApoC-III model. The model identified disease status as a covariate on K_{out} and IC_{50} , with FCS patients having 51% lower K_{out} and 80% increase in IC_{50} compared to healthy volunteers (HV). The Applicant's model estimated a 30% increase in IC_{50} in ADA-positive subjects with an ADA titer of 50.

Table 121. Parameter Estimates of the Final Octreotide Exposure-ApoC-III Model

Parameter Name	Estimated Value (%RSE)
First-order Elimination Rate (K_{out} , 1/h) [†]	0.0121 (8.4)
Covariate of Patients with HTG and CVD on K_{out}	0.289 (12.6)
Covariate of Patients with FCS on K_{out}	0.449 (25.7)
Concentration at Half-Maximal Drug Effect (IC_{50} , ng/mL) [‡]	0.247 (7.6)
Covariate of Patients with HTG and CVD on IC_{50}	1.11 (10.4)
Covariate of Patients with FCS on IC_{50}	1.8 (17.1)
Covariate of ADA Status on IC_{50}	1.3 (5.5)
Covariate of ADA Titer on IC_{50}	0.325 (10.5)
Maximum Inhibitory Effect (fraction)	0.961 (0.3)
Between Subject Variability K_{out} (%)	84.6 (7.6)
Between Subject Variability for IC_{50} (%)	94.5 (4.0)
Residual Unexplained Variability (Proportional, ADA Negative) (%)	25.3 (1.3)
Residual Unexplained Variability (Proportional, ADA Positive) (%)	33.3 (2.6)

ADA = anti-drug antibodies, CVD = cardiovascular disease, FCS = familial chylomicronemia syndrome, HTG = hypertriglyceridemia, RSE = relative standard error.

Note: PK parameters were fixed to the updated individual PK parameters (accounting for ADA effect).

$$^{\dagger}K_{out} = 0.0121 \cdot 0.289 \text{ (if HTG or CVD)} \cdot 0.449 \text{ (if FCS)}$$

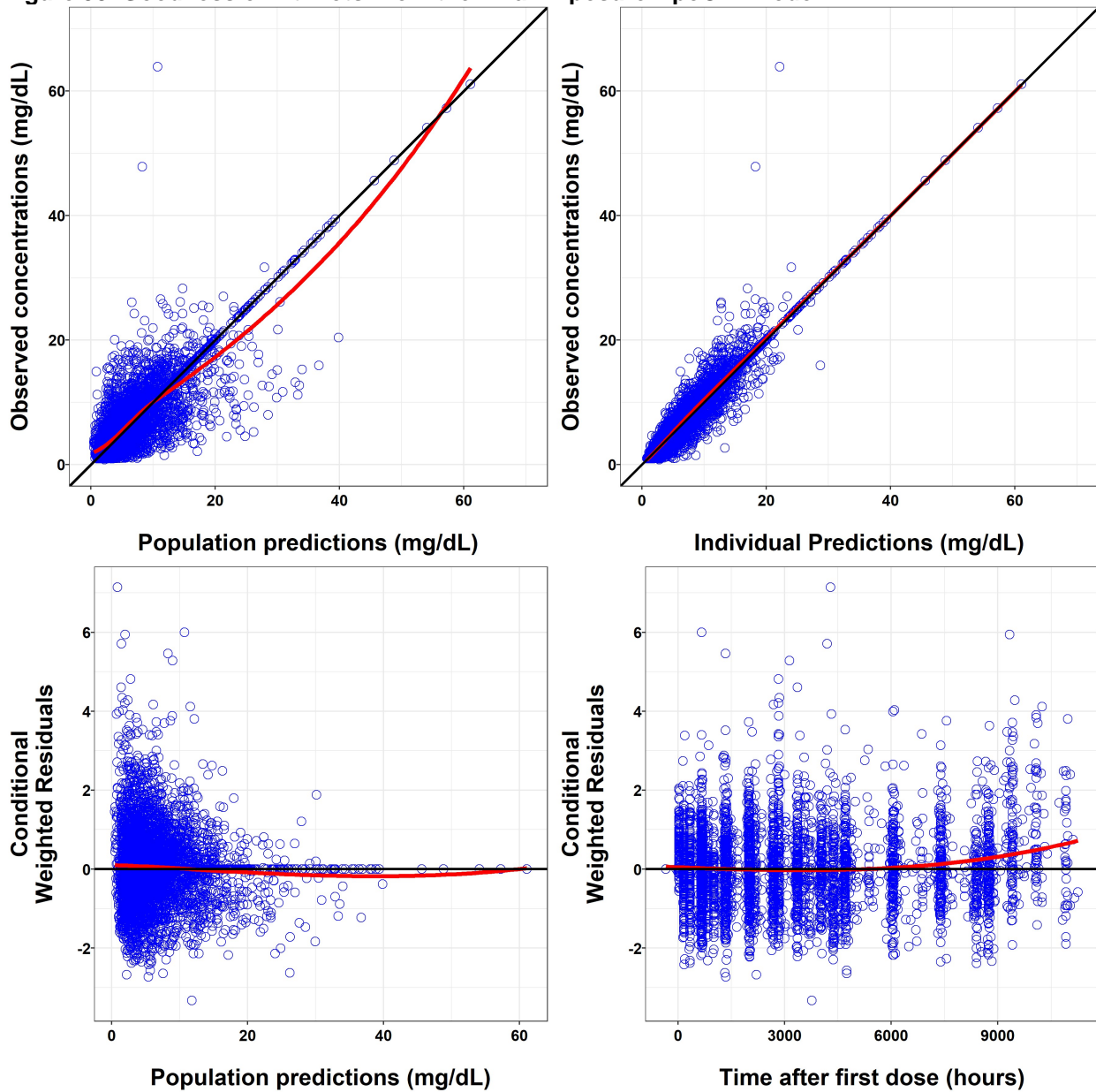
$$^{\ddagger}IC_{50} = 0.247 \cdot 1.11 \text{ (if HTG or CVD)} \cdot 1.8 \text{ (if FCS)} \cdot 1.3 \text{ (if ADA positive)} \cdot (ADATITER/50)^{0.325} \text{ (if ADATITER >0)}$$

Source: Applicant's Response to Information Request (September 10, 2024), Table 4, page 5.

Abbreviations: apo, apolipoprotein; IC_{50} , half maximal inhibitory concentration; K_{out} , first-order elimination rate

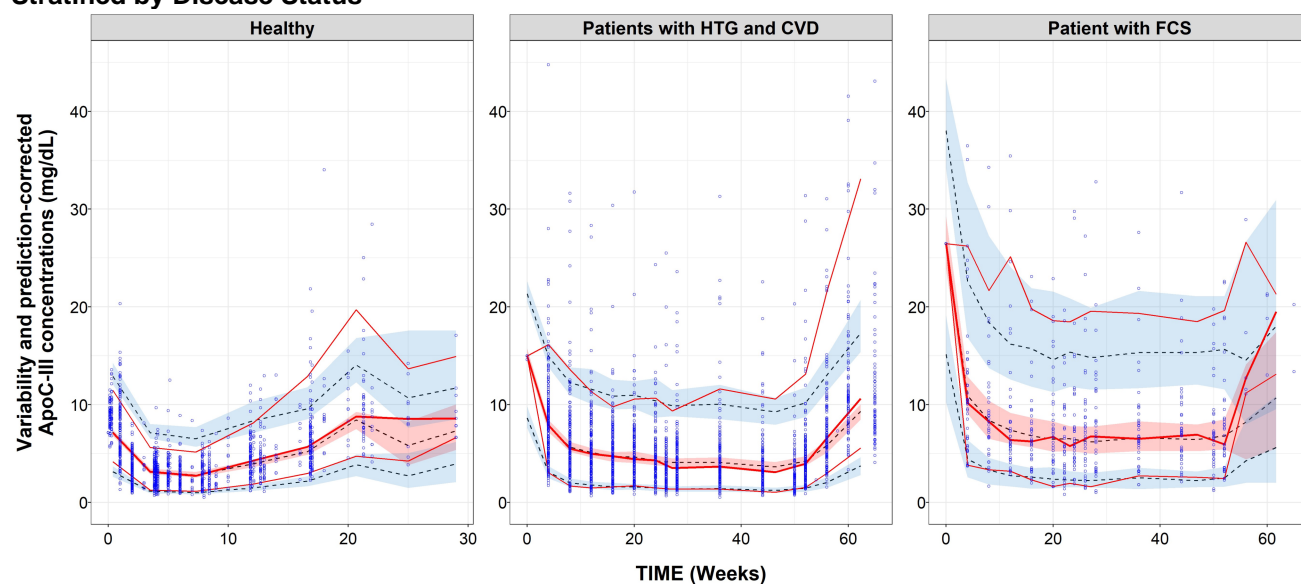
The GOF plots from the final exposure-ApoC-III model are shown in [Figure 58](#) and the pcVPC plots are shown in [Figure 59](#).

Figure 58. Goodness of Fit Plots From the Final Exposure-ApoC-III Model



Source: FDA reviewer
Note: CWRES=conditional weighted residuals; red lines represent loess smooth curves, and the black lines represent the line of unity ($y = x$) or $y = 0$.
Abbreviation: apo, apolipoprotein

Figure 59. Prediction-Corrected Visual Predictive Check From Final Exposure-ApoC-III Model, Stratified by Disease Status



Source: FDA reviewer

Note: blue dots: individual concentrations. Solid red lines: median, 5th and 95th percentiles of the prediction-corrected observations. Dashed black lines: predicted median, 5th and 95th percentiles. Shaded areas: 95% CI of the median, 5th and 95th percentiles predicted by the model.

Abbreviations: apo, apolipoprotein; CVD, cardiovascular disease; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia

Reviewer Comment and Assessment of the Exposure-ApoC-III Model

The Applicant's exposure-ApoC-III model is acceptable and adequately describes the individual observed ApoC-III concentrations and their variability in healthy volunteers, patients with FCS and patients with HTG and CVD.

- The PD parameters were estimated with an acceptable precision (<30% RSE). The estimated interindividual random error (η -) shrinkage was low ($\leq 30\%$) and acceptable for the reliable graphical assessment of covariate effects. The residual error (ϵ -) shrinkage was low (<6%), indicating the informativeness of the GOF plots to diagnose structural and residual error model misspecifications. The GOF plots show that the exposure-ApoC-III model fitted the observed data well with no critical trends or bias in the predicted versus the observed concentrations of ApoC-III and in the CWRES versus predictions or time from all studies and olezarsen dose levels.
- The pcVPC plots, stratified by disease status, indicate that the Applicant's exposure-ApoC-III model reasonably captures and describes the observed median ApoC-III concentrations and their variability from all studies with minimal bias.
- The Applicant did not provide the rationale and physiological explanation for including ADA status and titer on IC_{50} . The effect of ADA status/titer could be confounded by another unexplored covariate and appears to be driven only by Trial ISIS 678354-CS3 in FCS patients. The removal of ADA status and titer on IC_{50} from the exposure-ApoC-III model significantly increased the objective function value by 129 points (for 2 degrees of freedom [df]). The model without ADA status and titer effect did not change the estimated BSV for IC_{50} or the estimated PD model parameters, except for the effect of FCS disease on IC_{50}

which increased from 1.8 to 2.54 (i.e., 41% difference in the parameter estimate), suggesting that FCS patients are estimated to have 154% increase in IC₅₀ (IC₅₀ of 0.63 ng/mL) compared to HV (IC₅₀ of 0.247 ng/mL).

14.5.2.2. Exposure-TG Model

The exposure-TG model consisted of an indirect response model with a stimulatory drug effect on TG removal (elimination) rate constant (K_{out}). The drug effect on K_{out} was described as an E_{max} function with maximum effect (E_{max}) and a concentration at half maximum effect (EC₅₀). BSV terms were included on the K_{out}, E_{max} and EC₅₀ parameters. A proportional error model was used to describe the RUV of TG concentrations, with separate RUV estimated for patients with FCS and subject without FCS (including HV).

[Table 122](#) summarizes the parameter estimates of the final exposure-TG model. The model identified disease status as a covariate on K_{out} and EC₅₀. Patients with HTG or CVD experienced an approximate 61% reduction in K_{out} compared to HV or FCS patients. Patients with FCS have 619% increase in EC₅₀ compared to HV or patients with HTG or CVD. The Applicant's model estimated an increase in EC₅₀ with an ADA titer above 50.

Table 122. Parameter Estimates of the Final Olezarsen Exposure-TG Model

Parameter Name	Estimated Value (%RSE)
First-order Elimination Rate (K _{out} , 1/h) [†]	0.00307 (9.9)
Covariate of Patients with HTG and CVD on K _{out}	0.348 (13.6)
Concentration at Half-Maximal Drug Effect (EC ₅₀ , ng/mL) [‡]	1.48 (14.9)
Covariate of Patients with FCS on EC ₅₀	7.19 (35.9)
Covariate of ADATITER on EC ₅₀	0.211 (38.5)
Maximum Stimulatory Effect (E _{max} , fraction)	3.05 (7.4)
Between Subject Variability K _{out} (%)	72.9 (11.1)
Between Subject Variability for EC ₅₀ (%)	167 (6.4)
Between Subject Variability E _{max} (%)	54.7 (9.7)
Residual Unexplained Variability (Proportional, non-FCS) (%)	27.4 (1.2)
Residual Unexplained Variability (Proportional, FCS) (%)	45.7 (3.5)

ADA = anti-drug antibodies, CVD = cardiovascular disease, FCS = familial chylomicronemia syndrome, HTG = hypertriglyceridemia, RSE = relative standard error.

Note: PK parameters were fixed to the updated individual PK parameters (accounting for ADA effect).

[†]K_{out} = 0.00307 · 0.348 (if HTG or CVD)

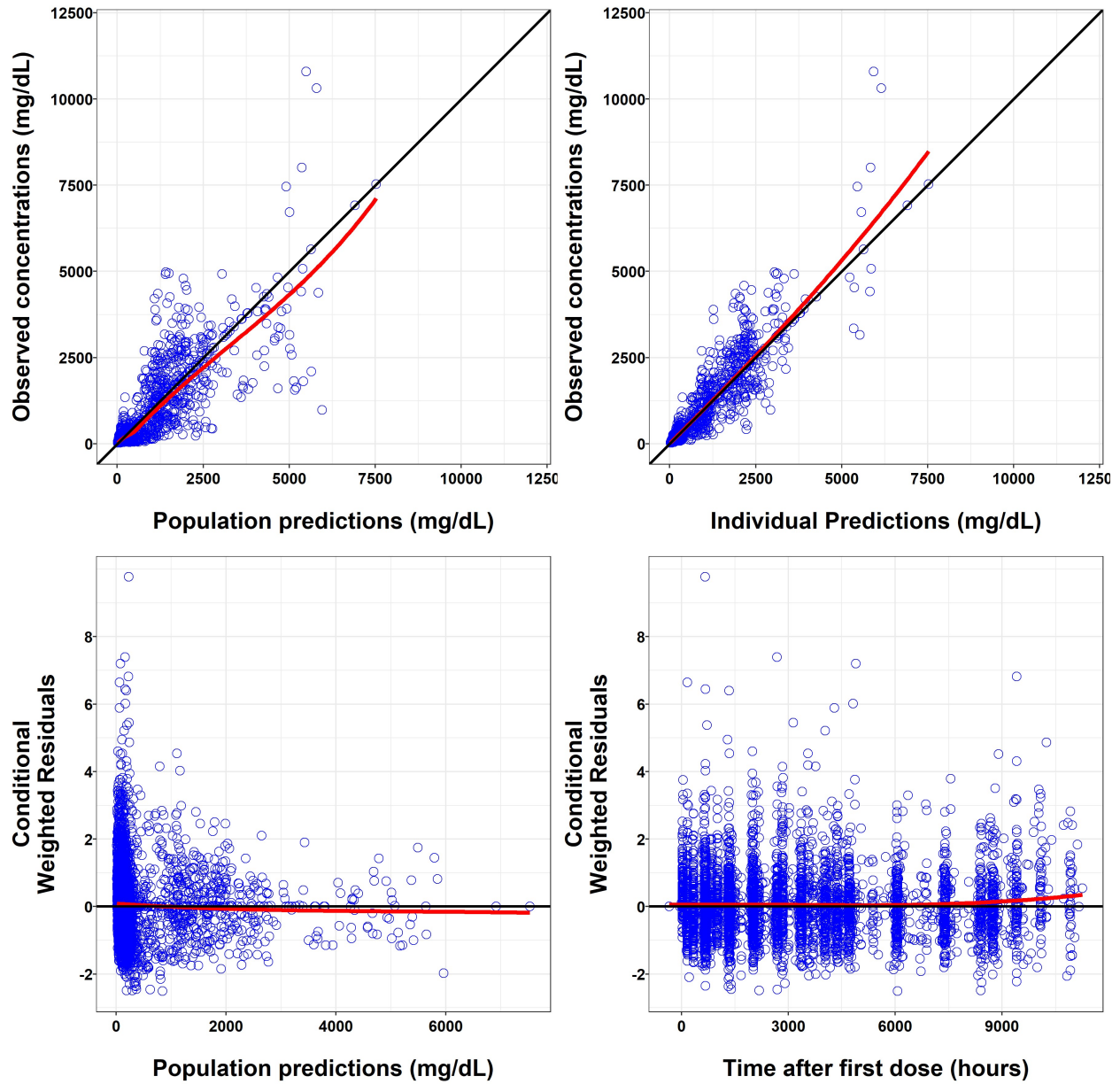
[‡]EC₅₀ = 1.48 · 7.19 (if FCS) · (ADATITER/50)^{0.211} (if ADATITER >0)

Source: Applicant's Response to Information Request (September 10, 2024), Table 5, page 5.

Abbreviations: EC₅₀, concentration at half maximum effect; K_{out}, first-order elimination rate; TG, triglycerides

The GOF plots from the final exposure-ApoC-III model are shown in [Figure 60](#) and the pcVPC plots are shown in [Figure 61](#).

Figure 60. Goodness of Fit Plots From the Final Exposure-TG Model

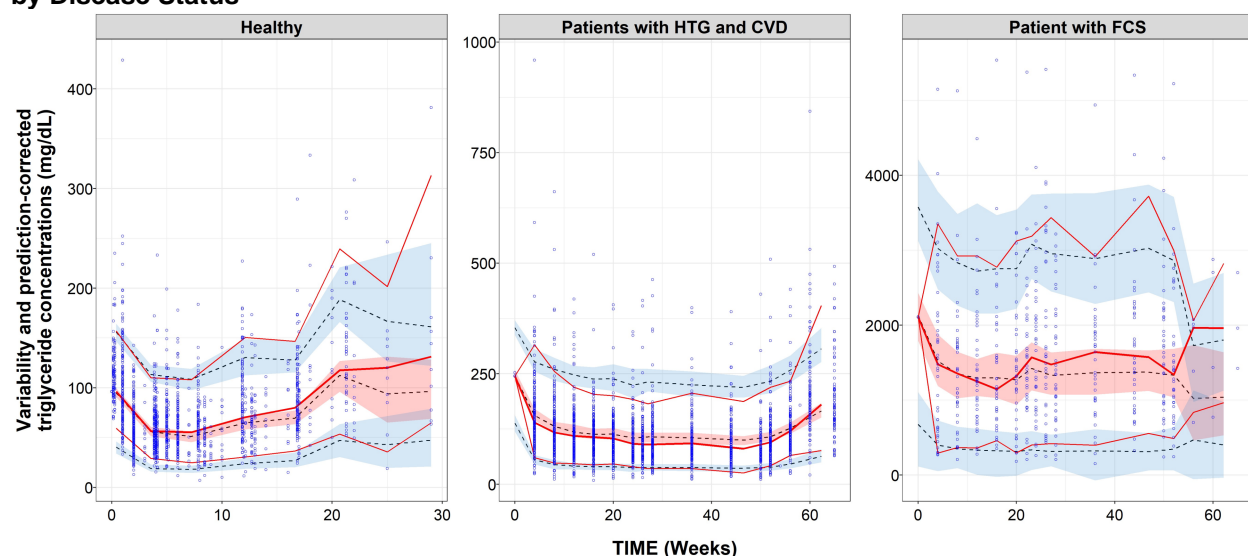


Source: FDA reviewer.

Note: CWRES=conditional weighted residuals; red lines represent loess smooth curves, and the black lines represent the line of unity ($y = x$) or $y = 0$.

Abbreviations: TG, triglycerides

Figure 61. Prediction-Corrected Visual Predictive Check From Final Exposure-TG Model, Stratified by Disease Status



Source: FDA reviewer.

Note: blue dots: individual concentrations. Solid red lines: median, 5th and 95th percentiles of the prediction-corrected observations. Dashed black lines: predicted median, 5th and 95th percentiles. Shaded areas: 95% CI of the median, 5th and 95th percentiles predicted by the model.

Abbreviations: CVD, cardiovascular disease; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; TG, triglycerides

Reviewer Comment and Assessment of the Exposure-TG Models

The Applicant's exposure-TG model is acceptable and reasonably describes the individual observed TG concentrations and their variability in healthy volunteers, patients with FCS and patients with HTG and CVD.

- The PD parameters were estimated with an acceptable precision (<30% RSE), with a relatively higher relative standard error (%RSE) of 36% for the estimated effect of FCS disease on EC_{50} . The estimated interindividual random error (η -) shrinkage was low (18%) for EC_{50} and acceptable for the reliable graphical assessment of covariate effects. The η -shrinkages were relatively high for K_{out} (46%) and E_{max} (42%) parameters. The residual error (ϵ -) shrinkage was low (<3%), indicating the informativeness of the GOF plots to diagnose structural and residual error model misspecifications. The GOF plots show that the exposure-TG model fitted the observed data well with no critical trends or bias in the predicted versus the observed concentrations of TG and in the CWRES versus predictions or time from all studies and olezarsen dose levels.
- The pcVPC plots, stratified by disease status, indicate that the Applicant's exposure-TG model reasonably captures and describes the observed median TG concentrations and their variability from all studies with minimal bias.
- The Applicant did not provide the rationale and physiological explanation for including ADA titer on EC_{50} . The removal of ADA titer on EC_{50} from the exposure-TG model did not significantly increase the objective function value (7.3 points for 1 df). The model without ADA status and titer effect did not change the estimated BSV for EC_{50} or the estimated PD model parameters (the estimated effect of FCS on EC_{50} increased by 13%). Olezarsen EC_{50}

was estimated to 12 ng/mL in the model without ADA titer effect versus 10.6 ng/mL in the Applicant's final exposure-TG model.

14.5.3. Application of the PK and Exposure-Response Models

The PK and exposure-response models were used to perform population simulations to support dose selection in patients with FCS. Simulations were performed for the following scenarios:

- 50 mg olezarsen Q4W for 13 doses (364 days) and every month (Q1M) for 12 doses (360 days).
- 80 mg olezarsen Q4W for 13 doses (364 days) and Q1M for 12 doses (360 days).

Figure 62 shows a trend towards a marginally higher percentage change from baseline (CFB) in ApoC-III and TG for the 80 mg compared to the 50 mg doses, with overlapping 95% CIs for the percent CFB in TG concentrations.

Figure 63 shows that the PK, ApoC-III, and TG profiles for Q4W and Q1M dosing overlap following first dose and at steady-state with a marginal difference in the percent CFB in ApoC-III and TG concentrations at the end of the dosing interval for the Q1M.

Figure 62. Predicted Olezarsen, ApoC-III, and TG Concentration-Time Profiles for 50 mg and 80 mg Q4W

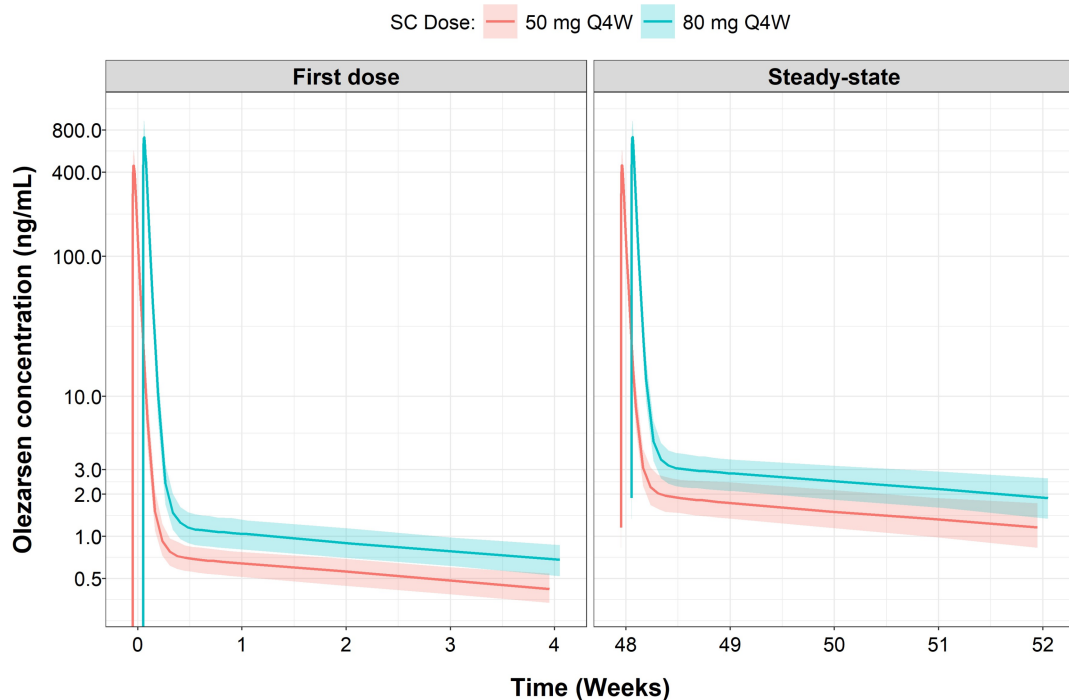
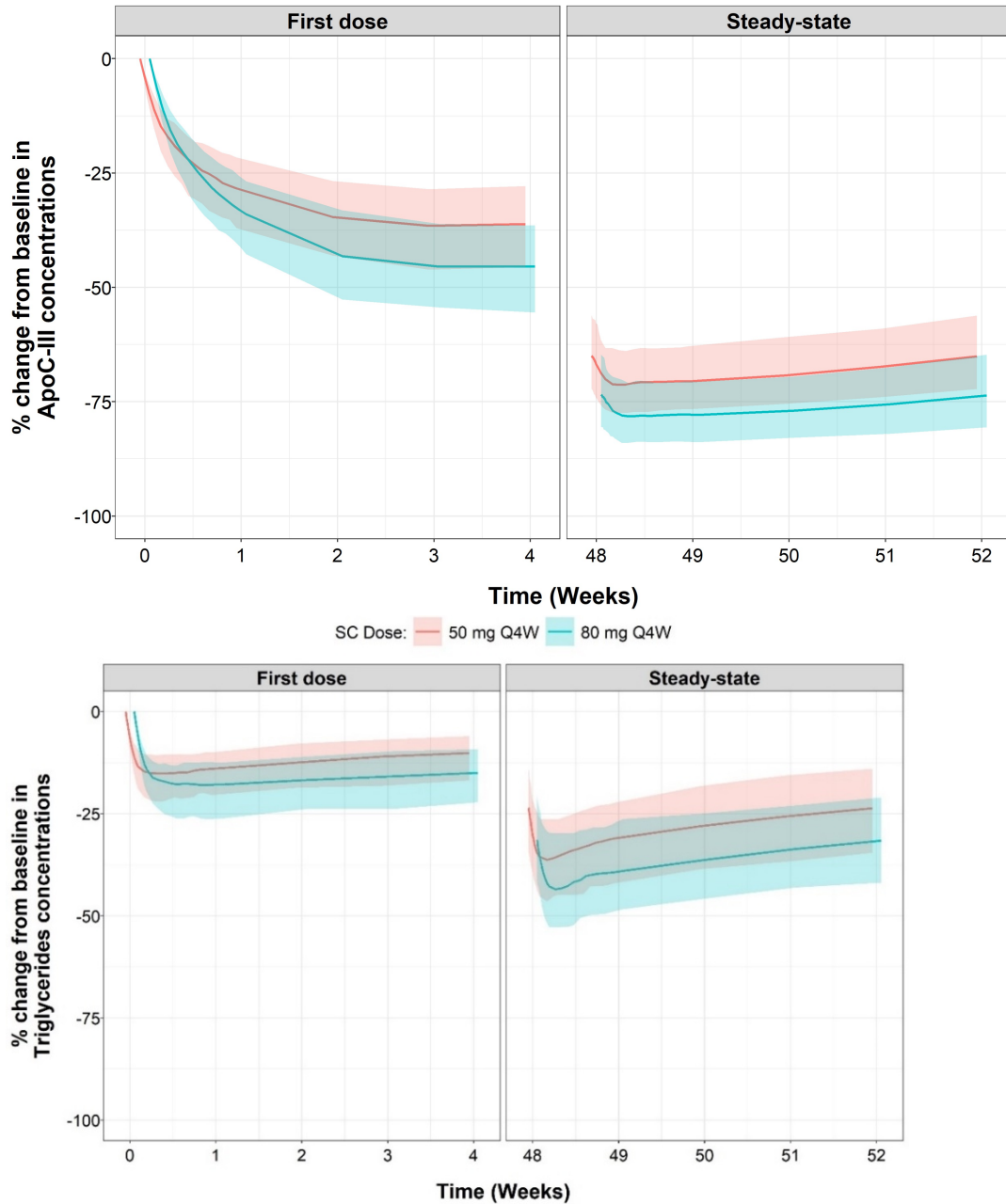


Figure 62 continued

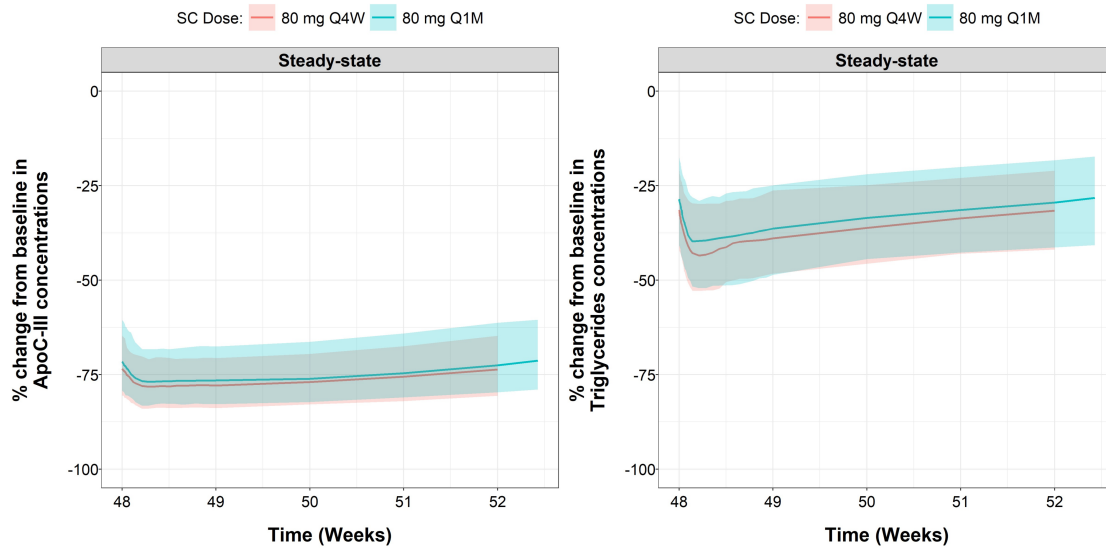


Source: FDA reviewer

Note: Solid lines: median of the simulated observations obtained from Monte-Carlo simulations. Shaded areas: 95% CI of the simulated median observations obtained from Monte-Carlo simulations. The simulations consisted of 1000 replicates of a virtual FCS population with the same demographic characteristics as study ISIS 678354-CS3 (n=43) and ADA negative status.

Abbreviations: ADA, antidrug antibody; apo, apolipoprotein; CI, confidence interval; FCS, familial chylomicronemia syndrome; Q4W, every four weeks; SC, subcutaneous; TG, triglycerides

Figure 63. Predicted ApoC-III and TG Concentration-Time Profiles for 80 mg Q4W and Q1M



Source: FDA reviewer

Note: Solid lines: median of the simulated observations. Shaded areas: 95% CI of the simulated median observations obtained from Monte-Carlo simulations (1000 replicates of a virtual FCS population with the same demographic characteristics as study ISIS 678354-CS3 (n=43)).

Abbreviations: apo, apolipoprotein; CI, confidence interval; FCS, familial chylomicronemia syndrome; Q1M, every 30 days; Q4W, every four weeks; SC, subcutaneous; TG, triglycerides

Reviewer Comment

The simulations from the PK and exposure-response models were reproducible and suggest that the 80 mg olezarsen administered Q4W or Q1M are acceptable and estimated to achieve, at the end of the dosing interval ($C_{trough,ss}$), a percent reduction from baseline in ApoC-III of 73.5% for Q4W or 71.6% for Q1M, and percent reductions from baseline in TG of 29.4% for Q4W and 28.6% for Q1M, in patients with FCS. According to the exposure-TG modeling and simulation, 50 mg and 80 mg olezarsen administered Q4W are estimated to achieve, at steady-state exposure and the end of the dosing interval, a median percent reduction from baseline in TG of 23.4 versus 29.4%, in patients with FCS. [Figure 62](#) shows a trend towards a marginally higher percentage CFB in TG for the 80 mg compared to the 50 mg doses, with overlapping 95% CIs for the percent CFB in TG concentrations.

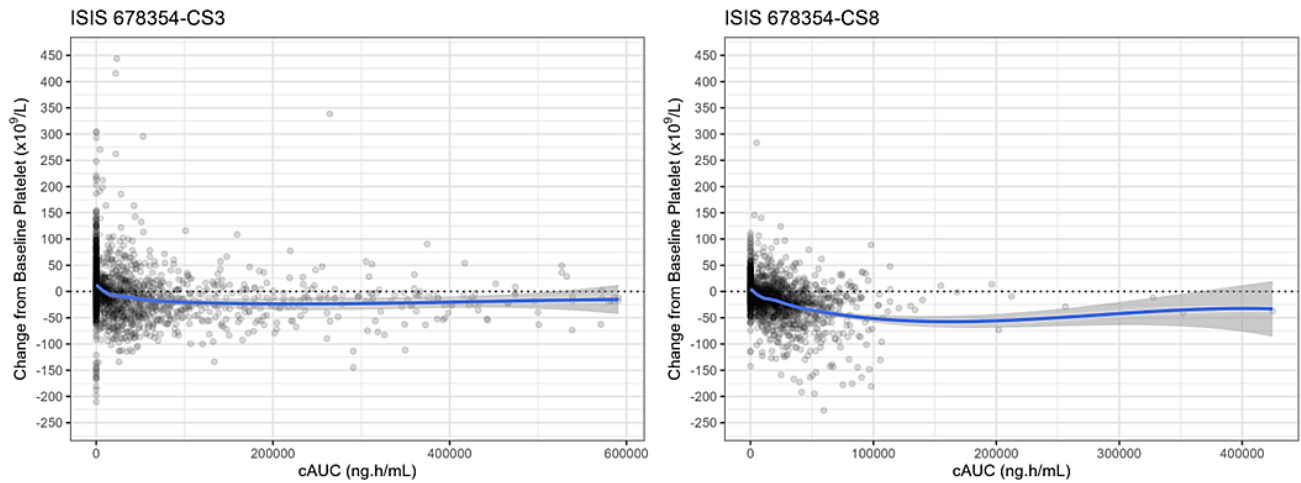
14.5.4. Exploratory Exposure-Safety Analyses

14.5.4.1. Exposure-Platelet Count Relationship

The Applicant performed exploratory analysis to evaluate the relationship between the CFB in platelet count versus cumulative AUC (cAUC) and C_{max} in Trials ISIS 678354-CS3 and ISIS 678354-CS8, concluding that there were no substantial trends in the observed change from baseline ([Figure 64](#)) or the maximum decrease from baseline in platelet count across the entire range of cumulative AUC or C_{max} .

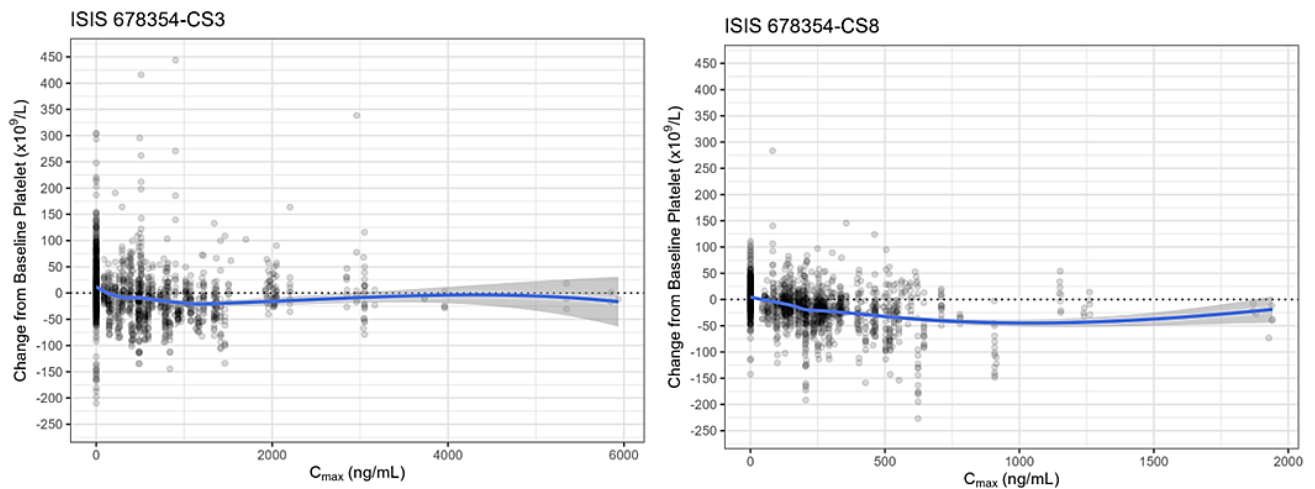
Figure 64. Change From Baseline in Platelet Count vs. Cumulative AUC and C_{max} , Stratified by Study

A. Change from baseline in platelet count versus cumulative AUC



(Figure 64: continued)

B. Change from baseline in platelet count versus C_{max}



Source: Applicant's Response to Information Request (September 5, 2024), Figures 21 to 24, pages 27 to 30

Note: Each circle represents a matched observed platelet value and model-predicted exposure metric. The solid line (blue): fit from a LOESS smoother with the 95% confidence interval as indicated by the shaded grey area. All placebo patients have an exposure metric value of 0.

Abbreviations: AUC, area under the concentration-time curve; cAUC, cumulative area under the concentration-time curve; C_{max} , maximum plasma concentration

Reviewer Comment

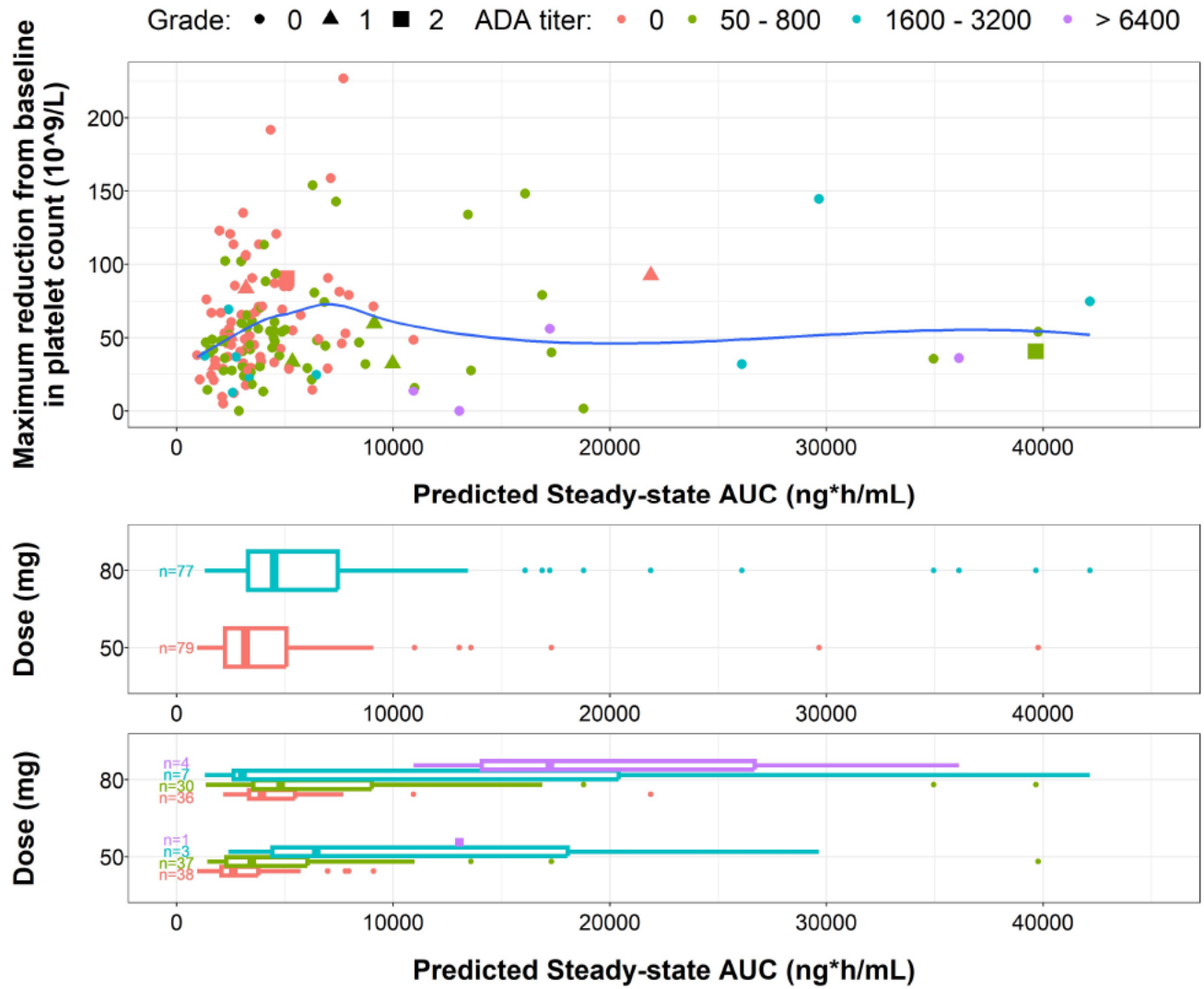
The Applicant exploratory analysis evaluating the relationship between the CFB in platelet count versus cumulative AUC (cAUC) is difficult to interpret due to different duration of treatment or follow-up between patients and the cAUC was not standardized to the duration of treatment at the time of measured platelet count. As an alternative exploratory analysis, the reviewers explored the relationship between the maximum decrease in platelets counts and steady-state exposure metrics (AUC_{ss} , $C_{trough,ss}$, $C_{max,ss}$), predicted using individual PK parameters at the time

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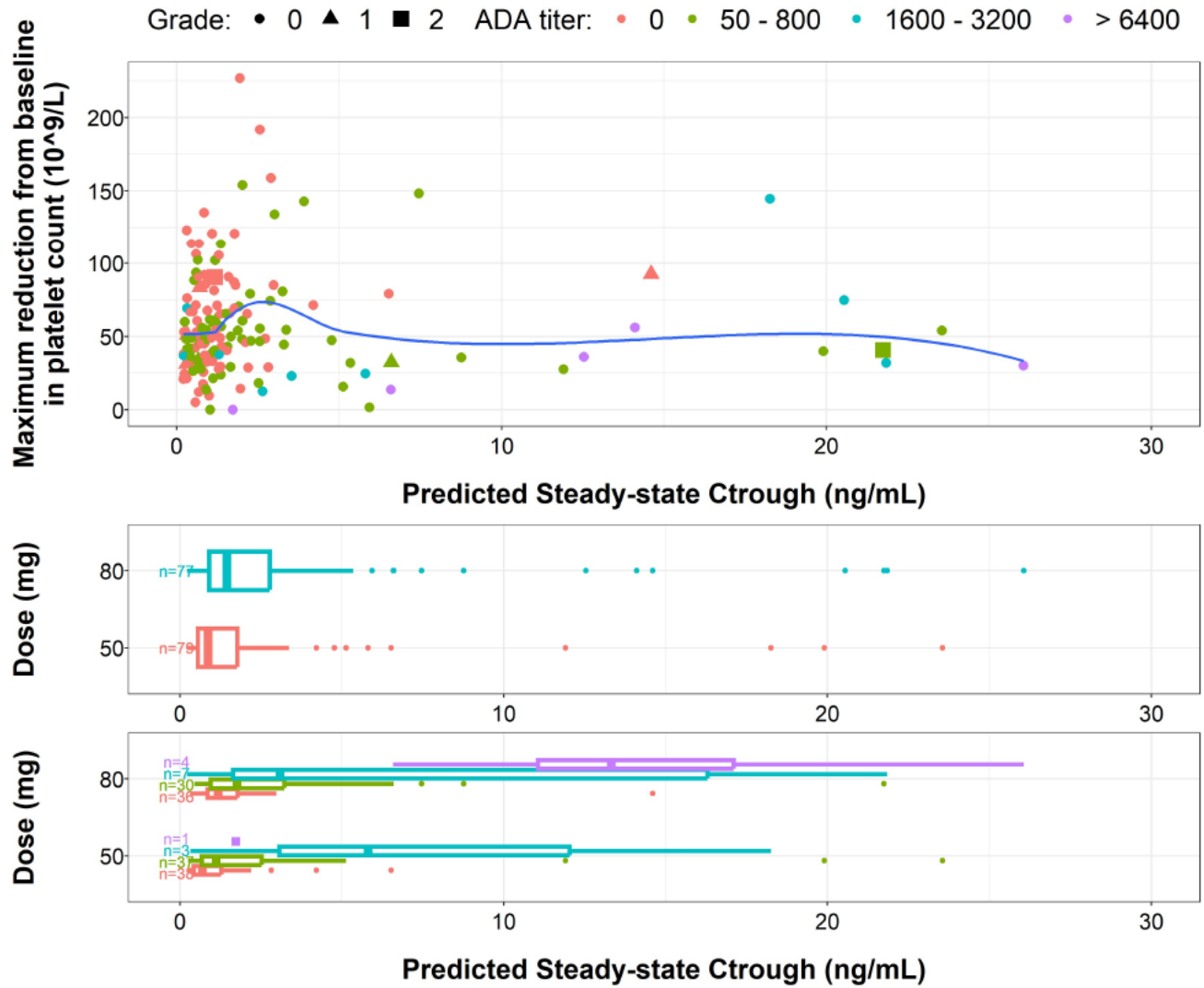
Tryngolza (olezarsen sodium)

associated with the maximum decrease from baseline in platelets counts (to account for the effect of ADA titer on exposure metrics). [Figure 65](#) shows that the relationship between olezarsen exposure metrics and the maximum reduction in platelet count (from merged Trials ISIS 678354-CS3 and -CS8) is relatively shallow, with most patients experiencing less than grade 1 thrombocytopenia, and most patients with highest maximum decrease in platelets counts having no ADA or maximum ADA titer lower or equal 800. A similar pattern was observed for percent maximum decrease from baseline in platelets counts and exposure-metrics.

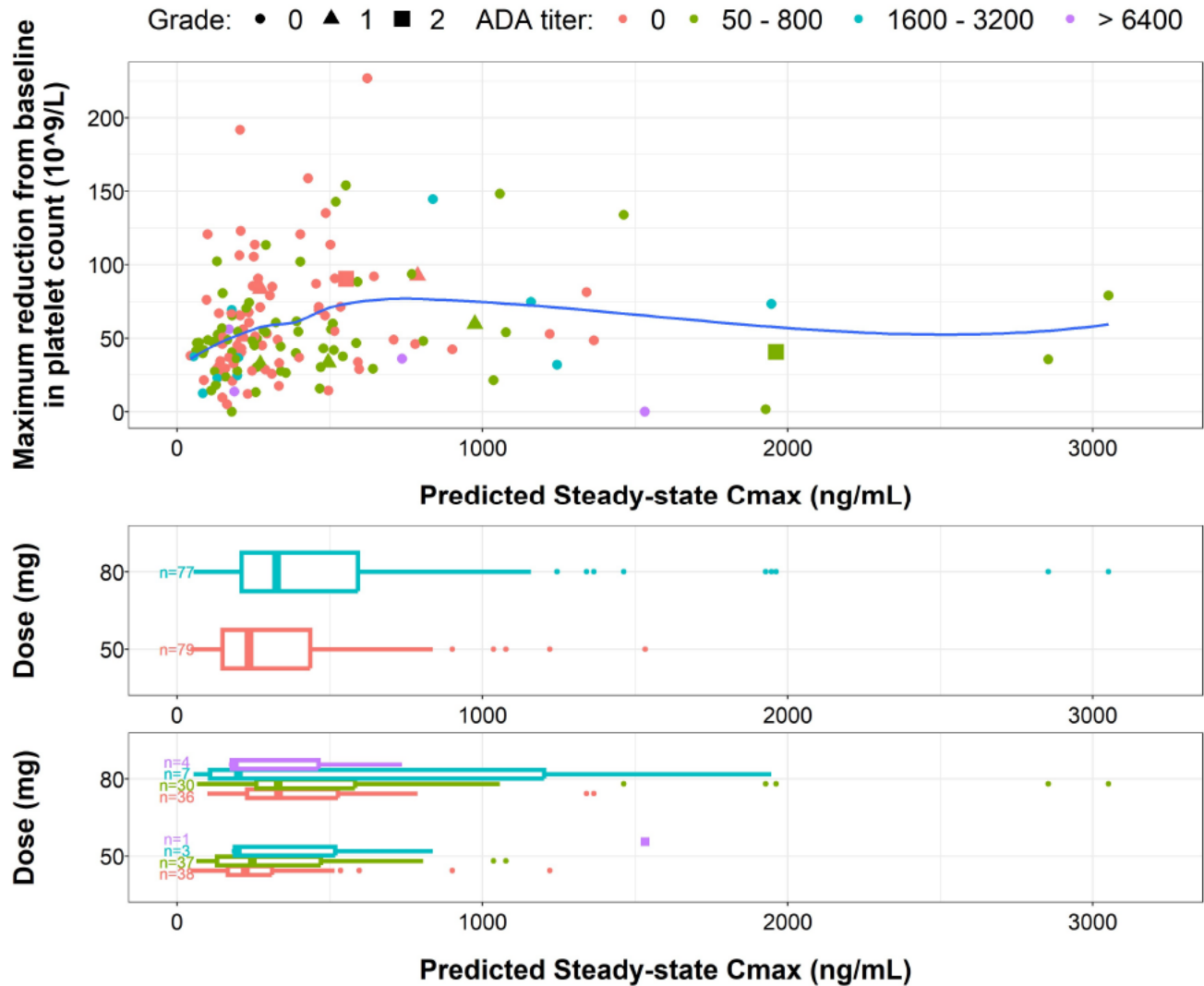
Figure 65. Maximum Change From Baseline in Platelet Count vs. Steady-State Exposure Metrics



(Figure 65 continued)



(Figure 65: continued)



Source: FDA reviewer.

Note: the absolute values of the maximum reduction from baseline in platelets count are represented. Each subject (symbol) from study ISIS 678354-CS3 or -CS8 is contributing by a single value of maximum reduction from baseline in platelets and the associated PK model-predicted steady-state exposure metric. Symbol shape: represents the grade of thrombocytopenia for a subject. Symbol color: represents the maximum ADA titer group for a subject.

Abbreviations: ADA, antidrug antibody; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration

14.5.4.2. Exposure-Hypersensitivity Relationship

In Trial ISIS 678354-CS3 and -CS8, 10 patients (6.5%) experienced at least one treatment-emergent adverse event (TEAE) by hypersensitivity FDA Medical Dictionary for Regulatory Activities Query (FMQ) broad scope definition.

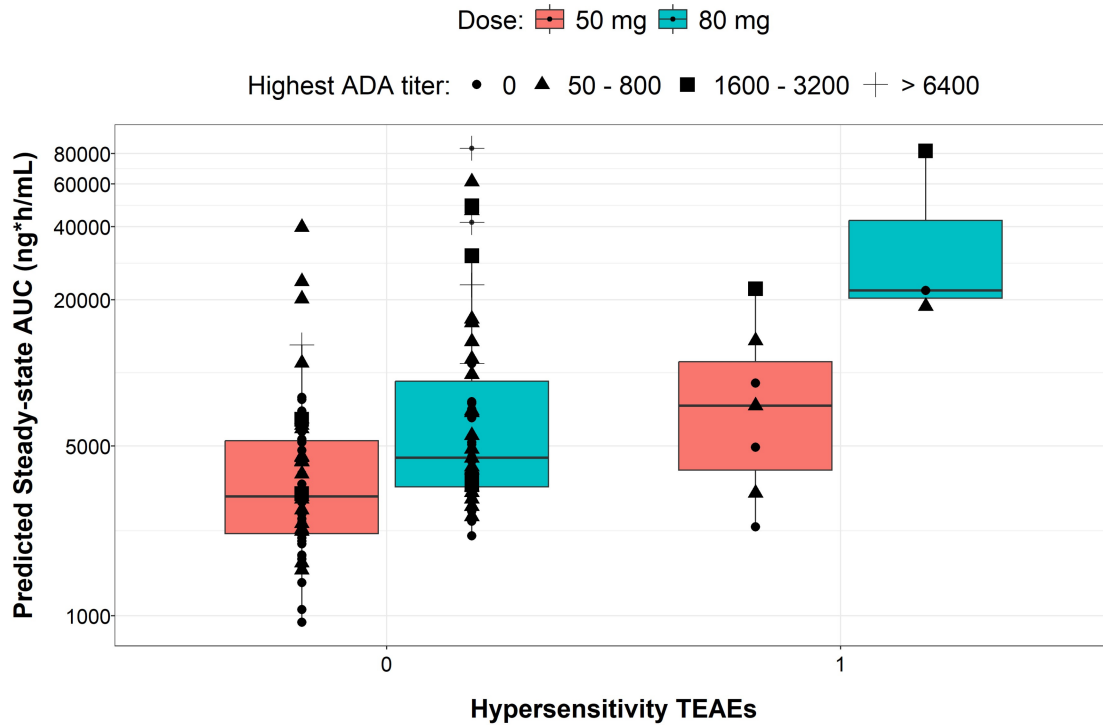
The reviewer assessment of the relationship between olezarsen exposure (AUC_{ss}, C_{max,ss}, and C_{trough,ss}) and the occurrence of hypersensitivity TEAEs (broad scope), observed a slight trend between higher AUC_{ss} or C_{trough,ss} and the occurrence of hypersensitivity TEAEs. However, this

trend was driven mostly by three patients receiving the 80 mg dose (Figure 66). No trend was observed between $C_{max,ss}$ and the occurrence of hypersensitivity TEAEs.

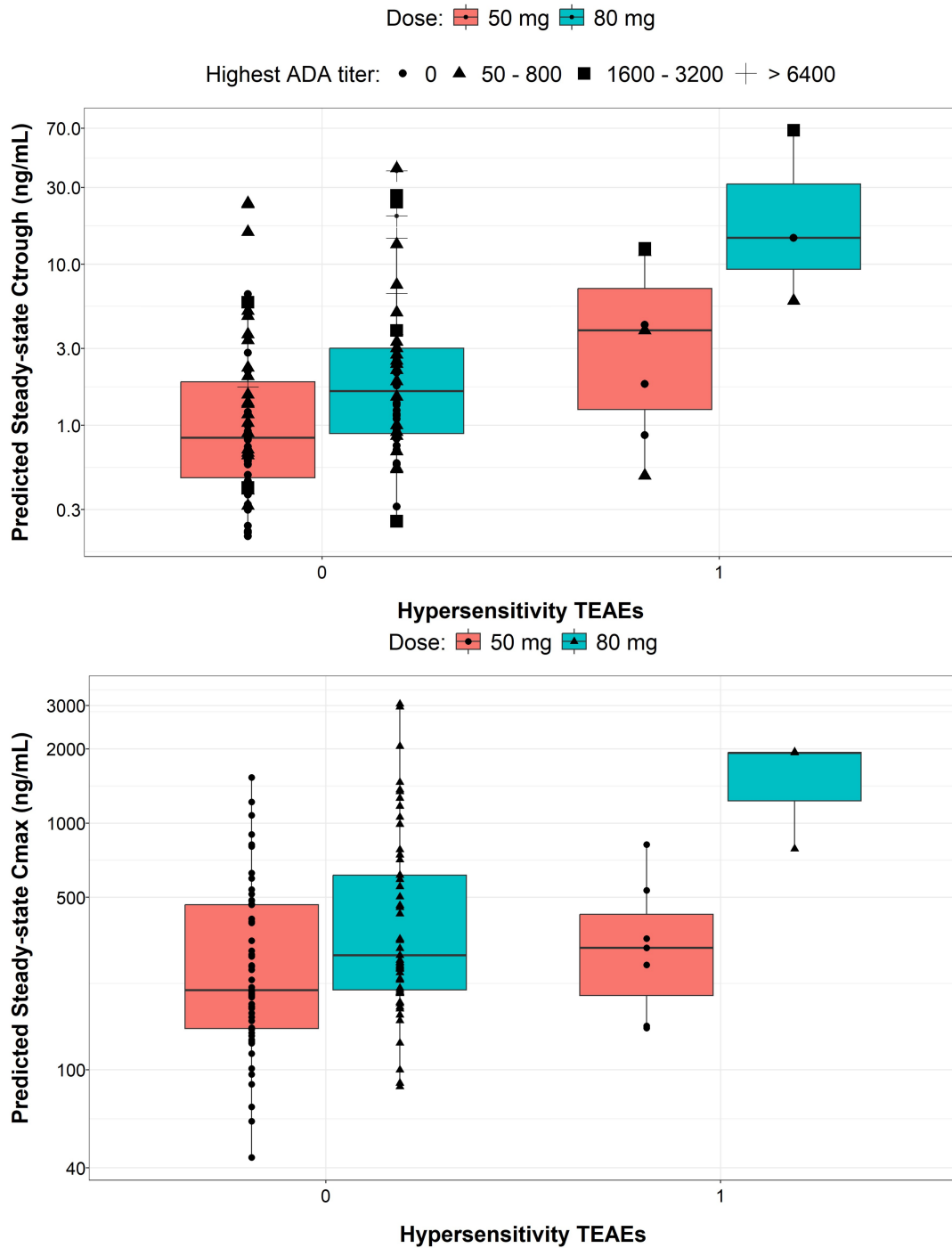
Figure 66 shows that the steady-state exposure metrics are overlapping between patients who experienced hypersensitivity TEAEs and those who did not experience hypersensitivity TEAEs.

Three patients in the 80 mg treatment arm of Trial ISIS 678354-CS3 and -CS8, who have among the highest exposure metrics, were driving the positive relationship estimated between olezarsen AUC_{ss} or $C_{trough,ss}$ and the occurrence of hypersensitivity TEAEs, according to a logistic regression analysis. Amongst these three patients, one patient had negative ADA titer, and two patients had ADA titers of 1600 and 3200, respectively.

Figure 66. Olezarsen Exposure Metrics by Hypersensitivity TEAEs, Stratified by Dose



(Figure 66 continued)



Source: FDA reviewer

Note: Boxplots are colored by dose. Shape of symbols: represent the maximum ADA titer group for each subject.

Abbreviations: ADA, antidrug antibody; AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; Ctrough, trough plasma concentration; TEAE, treatment-emergent adverse event

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Trial ISIS 678354-CS3

15.1.1. Clinical Study Protocol Synopsis

The following is the Applicant's protocol synopsis of Trial ISIS 678354-CS3 from protocol amendment 9 (August 2, 2023), which was the final version of the protocol prior to the data cutoff.

Title

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

Landmark Dates

- First subject Dosed: December 17, 2020
- Last subject Enrolled: July 11, 2022
- Last subject, Last Dose: June 20, 2023
- Last subject, Last Visit: Subjects still in follow-up time at data cut-off
- Data Cutoff: July 14, 2023
- Database Lock Date: August 30, 2023

Objectives

Primary

To evaluate the efficacy of olezarsen as compared to placebo on the percent change in fasting TG from baseline.

Secondary

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

- Percent change in fasting ApoC-III from baseline
- Proportion of subjects who achieve $\geq 40\%$ reduction in fasting TG from baseline
- Percent change in fasting ApoB-48 from baseline
- Percent change in fasting non-HDL-C from baseline
- Adjudicated AP event rate in subjects with a prior history of pancreatitis within 10 years prior to screening
- Adjudicated AP event rate
- Proportion of subjects who achieve $\geq 70\%$ reduction in fasting TG from baseline
- Proportion of subjects who achieve fasting TG ≤ 880 mg/dL (10 mmol/L)
- Adjudicated AP event rate in subjects with two or more events of adjudicated AP in 5 years prior to enrollment
- Proportion of subjects who achieve fasting TG ≤ 500 mg/dL (5.7 mmol/L)

Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study. Eligible subjects will enter an approximately 4-week, but no more than 8-week, screening period that includes an at least 2-week diet stabilization/run-in period for subjects not already on a stable diet, and an approximately 2-week qualification period. Following qualification, approximately 60 eligible subjects will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 2:1 to receive olezarsen or placebo in a 53-week treatment period.

Subjects in Cohort A will receive 50 mg of olezarsen Q4W or matching volume of placebo (0.5 mL) for Weeks 1 through 49 of the treatment period. Subjects in Cohort B will receive 80 mg olezarsen Q4W or matching volume of placebo (0.8 mL) for Weeks 1 through 49 of the treatment period. Randomization will be stratified by: (1) prior history of pancreatitis (within 10 years prior to screening); and (2) previous treatment with volanesorsen. Dietary counseling will commence at the start of the diet stabilization period and will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 53 visit, eligible subjects may elect to enroll in an open-label extension (OLE) study pending study approval by the institutional review board/independent ethics committee and the appropriate regulatory authority. Subjects not participating in the OLE will enter the 13-week post-treatment evaluation period. The primary endpoint for the study will be evaluated after the last subject has completed the Week 53/ET visit and will be based on the percent change in fasting TG from baseline at the primary analysis time point (Month 6).

The subjects, investigators, study staff, and the Applicant 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.

Population

Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Aged ≥ 18 years at the time of informed consent
3. A diagnosis of Familial Chylomicronemia Syndrome (type 1 Hyperlipoproteinemia) by documentation of confirmed homozygote, compound heterozygote or double heterozygote for loss-of-function mutations in type 1-causing genes (such as LPL, GPIHBP1, ApoA5, ApoC2, GPD1, or LMF1)
4. Fasting TG ≥ 880 mg/dL (10 mmol/L) at screening. If fasting TG is < 880 mg/dL up to two additional tests may be performed with any single test used to qualify
5. History of pancreatitis (defined as a recorded diagnosis of AP or hospitalization or emergency room (ER) visit for severe abdominal pain consistent with AP and for which no alternate diagnosis was made within 10 years prior to screening. Subjects without a recorded history of pancreatitis, or no recorded history within 10 years prior to screening, are also eligible but their enrollment will be capped at 35% (i.e., ≤ 21 of the 60 planned subjects)
6. Willing to follow a diet comprising ≤ 20 g fat per day during the study
7. Willing to complete all patient-reported outcome assessments throughout the study
8. Satisfy the following:

Females: must be non-pregnant and non-lactating and either:

Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);

Postmenopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);

Abstinent*; or

If engaged in sexual relations of child-bearing potential, agree to use a highly effective contraceptive method from the time of signing the informed consent form until at least 17 weeks after the last dose of study drug (olezarsen or placebo)

Males: Surgically sterile, abstinent*, or if engaged in sexual relations with a female of child-bearing potential, subject is utilizing a highly effective contraceptive method from the time of signing the informed consent form until at least 17 weeks after the last dose of study drug (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 subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception*

9. Atypical antipsychotic medications (e.g., olanzapine and clozapine) will be allowed if on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant through the end of their participation in this study
10. The following concomitant medications will be allowed if on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant through the end

of their participation in this study (occasional or intermittent use of over-the-counter (OTC) medications will be allowed at investigator's discretion):

Statins, omega-3 fatty acids (prescription and OTC), fibrates, or other lipid-lowering medications. Subjects taking OTC omega-3 fatty acids should make every effort to remain on the same brand through the end of the study

Antidiabetic medications

Antihypertensive medications

Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) and regular clinical monitoring is performed

Tamoxifen, estrogens or progestins

Exclusion Criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening) or physical examination
2. AP within 4 weeks prior to screening
3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion:

Platelet count $<100\text{K}/\text{mm}^3$ at screening or qualification. If the platelet count is $<100\text{K}/\text{mm}^3$ up to two additional tests may be performed to qualify at both screening and qualification
ALT or AST $>3.0 \times$ upper limit of normal (ULN)

Total bilirubin $>\text{ULN}$ unless due to Gilbert's syndrome

eGFR $<45 \text{ mL}/\text{min}/1.73 \text{ m}^2$ (as determined by the Chronic Kidney Disease Epidemiology formula for creatinine clearance; [Levey et al. 2009](#))

Urine protein/creatinine ratio (UPCR) $\geq 500 \text{ mg}/\text{g}$ or urine albumin/creatinine ratio (UACR) $\geq 300 \text{ mg}/\text{g}$

4. Uncontrolled arterial hypertension (blood pressure [BP] $>160/100 \text{ mmHg}$)
5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at screening
6. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 or active Covid-19 infection with or without therapy that will not be resolved by Study Day 1
7. Active infection with HIV, hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Subjects at screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor
8. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Subjects with a history of

other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor

9. Blood donation of 50 to 499 mL within 30 days of screening or of >499 mL within 60 days of screening
10. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer
11. Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of screening, or 5 half-lives, whichever is longer. This exclusion does not apply to vaccines
12. Concomitant medication/procedure restrictions:

Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening and during the study unless approved by the Sponsor Medical Monitor

Plasma apheresis within 4 weeks prior to screening or planned during the study

Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the investigator

Have any other conditions, which, in the opinion of the investigator would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study

Sample Size

- Approximately 60

Treatments

- Cohort A (n = 30): Subjects will be randomized 2:1 to receive 50 mg olezarsen or matching volume of placebo SC Q4W for Weeks 1-49. Administered SC 0.5 mL volume
- Cohort B (n = 30): Subjects will be randomized 2:1 to receive 80 mg olezarsen or matching volume of placebo SC Q4W for Weeks 1-49. Administered SC 0.8 mL volume

Endpoints

Primary

- Percent change in fasting TG from baseline at 6 months (average of Weeks 23, 25, and 27) compared to placebo

Secondary

- Percent change in fasting TG from baseline at 12 months (average of Week 51 and 53) compared to placebo
- Percent change in fasting ApoC-III from baseline at 6 months compared to placebo
- Percent change in fasting ApoC-III from baseline at 12 months compared to placebo
- Proportion of subjects who achieve $\geq 40\%$ reduction in fasting TG from baseline at 6 months compared to placebo
- Percent change in fasting ApoB-48 from baseline at 6 months compared to placebo
- Percent change in fasting non-HDL-C from baseline at 6 months compared to placebo
- Adjudicated AP event rate during the treatment period (Week 1 through 53) compared to placebo, in subjects with a history of pancreatitis within 10 years prior to screening
- Adjudicated AP event rate during the treatment period (Week 1 through 53) compared to placebo
- Adjudicated AP event rate from Week 13 through 53 compared to placebo in subjects with a history of pancreatitis within 10 years prior to screening
- Adjudicated AP event rate from Week 13 to 53 compared to placebo
- Proportion of subjects who achieve $\geq 70\%$ reduction in fasting TG from baseline at 6 months compared to placebo
- Percent change in fasting non-HDL-C from baseline at 12 months compared to placebo
- Percent change in fasting ApoB-48 from baseline at 12 months compared to placebo
- Proportion of subjects who achieve fasting TG ≤ 880 mg/dL at 6 months compared to placebo
- Adjudicated AP event rate during the treatment period (Week 1 through 53) compared to placebo, in subjects with two or more events of adjudicated AP in 5 years prior to enrollment
- Adjudicated acute pancreatitis (AP) event rate from Week 13 to 53 compared to placebo, in subjects with two or more events of adjudicated AP in 5 years prior to enrollment
- Proportion of subjects who achieve fasting TG ≤ 500 mg/dL at 6 months compared to placebo

Exploratory

- Frequency and severity of patient-reported abdominal pain and other FCS-related symptoms (including physical fatigue, difficulty thinking and diarrhea), diet, and impacts, HRQoL, cognitive function, and ER visits, incidence of all-cause hospitalizations and total inpatient days, compared to placebo (discussed in Section [16.3](#) of this document)

Safety

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

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Procedures and Assessments

Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, olezarsen plasma trough concentrations, ADA testing, electrocardiogram (ECG), and patient-reported outcome (PRO) assessments will be performed according to the schedule of procedures in [Table 123](#) below.

Table 123. Schedule of Procedures, Trial CS3

Study Week	Screening		Treatment Period																	Follow-up Period			
	Run-in ^A	Qual	1	5 ^o	9 ^o	13 ^o	17 ^o	21 ^o	23/ET-L1 ^{o,R}	25/ET-L2 ^{o,R}	27/ET-L3 ^{o,R}	29 ^o	33 ^o	37 ^o	41 ^o	45 ^o	49 ^o	51/ET-L4 ^{o,R}	53/ET-L5 ^{o,R} or Tx ET ^o	40 ^{o,P}	80 ^{o,P}	130 ^{o,P} / Post-Tx ET	
Study Day	-28 to -15	-14 to -7	1	29	57	85	113	141	156	169	183	197	225	253	281	309	337	351	365	28 ^P	56 ^P	91 ^P	
Visit and Testing Window ± Days	0	0	-3 ^B	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
Informed Consent	X																						
Medical History ^C	X																						
FSH ^D	X																						
Hepatitis B, C, HIV	X																						
Genetic testing ^E	X																						
Inclusion/Exclusion Criteria	X	X																					
Body Weight and Height ^F	X		X							X									X			X	
Vital Signs	X		X	X		X		X		X		X		X		X			X			X	
Physical Examination	X		X			X				X				X					X			X	
12-lead ECG (triplicate)	X		X			X				X				X					X			X	
Pregnancy Test ^F	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Extended Urinalysis ^G	X		EVERY 14 DAYS (± 2 days) ^O					X	X		X		X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine ^{H, J}	X		EVERY 14 DAYS (± 2 days) ^O					X	X		X		X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel ^{I, J}	X		EVERY 14 DAYS (± 2 days) ^O					X	X		X		X	X	X	X	X	X	X	X	X	X	X
Hematology ^J	X	X	HEMATOLOGY PERFORMED EVERY 14 DAYS (± 2 days) ^O																			X	
Coagulation (aPTT, PT, INR)	X		X							X									X				
Lipid Panel ^I	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA1c, HOMA-IR, Fructosamine, Glycated Albumin			X			X				X									X			X	
hsCRP			X							X									X			X	
Anti-drug Antibody			X ^{O, Q}	X	X					X				X					X	X	X	X	
Plasma PK - ISIS 678354 ^K			X ^{O, Q}	X	X	X	X			X		X	X	X	X				X	X	X	X	

Study Week	Screening		Treatment Period																	Follow-up Period		
	Run-in ^A	Qual	1	5 ^o	9 ^o	13 ^o	17 ^o	21 ^o	23/ET-L1 ^{o,R}	25/ET-L2 ^{o,R}	27/ET-L3 ^{o,R}	29 ^o	33 ^o	37 ^o	41 ^o	45 ^o	49 ^o	51/ET-L4 ^{o,R}	53/ET-L5 ^{o,R} or Tx ET ^o	40 ^{o,P}	80 ^{o,P}	130 ^{o,P} / Post-Tx ET
Study Day	-28 to -15	-14 to -7	1	29	57	85	113	141	156	169	183	197	225	253	281	309	337	351	365	28 ^P	56 ^P	91 ^P
Visit and Testing Window ± Days	0	0	-3 ^B	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Archived Serum & Plasma Samples ^{L, L}			X			X			X	X	X			X		X			X			X
FCS Symptoms Two Week Recall	X																					
FCS Symptoms and Diet	DAILY DIARY																					
FCS Impacts; Pain Interference Short Form 8a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Severity (PGIS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Patient Global Impression of Change (PGIC)								X	X	X								X	X			
Health-related Quality of Life (PROMIS 29+2 Profile v2.1), PROMIS Cognitive Function 4a (optional)			X			X			X	X	X							X	X			
Assessment of ER Visits, Hospitalization and Inpatient Days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet/Alcohol Counseling ^M	X		X	X		X			X			X		X					X			X
Study Drug: SC Injection ^N			X	X	X	X	X	X		X		X	X	X	X	X	X					

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

Legend

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

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

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

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^D For confirmation of menopause at Screening per inclusion criteria

^E Height only required at Screening

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

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

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

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

^J If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 3 days and not later than 7 days). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator. Any case of a platelet count < 50,000/mm³ should be reported in an expedited fashion to the Sponsor

^K Refer to Appendix C for PK Sampling schedule

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

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

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

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

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

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

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

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

Source: Trial CS3 CSR

Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; CSR, clinical study report; ECG, electrocardiogram; ER, emergency room; ET, early termination; ET-L, early termination-landmark; FCS, familial chylomicronemia syndrome; FSH, follicle stimulating hormone; HbA1c, hemoglobin A1c; HOMA-IR, xx; INR, international normalized ratio; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; PROMIS, Patient-Reported Outcomes Measurement Information System; PT, prothrombin time; Qual, quality; SC, subcutaneous; TG, triglycerides; Tx, treatment; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

Statistical Plan

Sample Size Considerations

Based upon prior clinical trial experience with FCS subjects, the SD of the percent change from baseline in TGs is approximately 46%. With 14 subjects in each olezarsen treatment group and 14 in the pooled placebo group, there would be a 90% 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 subjects and no change in the placebo subjects. Approximately 60 subjects will be enrolled in this trial to account for potential early dropouts and to facilitate safety evaluations.

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

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

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

Analysis of the Primary Endpoint

The primary analysis of the primary endpoint is to compare the percent CFB to the primary analysis time point in fasting TG between each olezarsen treatment group vs. pooled placebo using an analysis of covariance (ANCOVA) model in the full analysis set (FAS). The ANCOVA model will include the effects of treatment (olezarsen 80 mg, olezarsen 50 mg, or placebo), two

randomization stratification factors (history of pancreatitis and previous treatment with volanesorsen), and log-transformed baseline TG. To account for potential heterogeneity in variance, the 95% CI of the treatment differences will be calculated using the robust variance estimator based on the Bell and McCaffrey method ([Imbens and Kolesar 2016](#)). If subjects have intercurrent event(s) before Week 23, e.g., treatment discontinuation, use of additional medication, changes in background or concomitant treatments, the treatment policy strategy will be implemented, the subjects' assessments post intercurrent events will continue to be collected and utilized in the primary analysis. Subjects with a missing TG value after discontinuation will have TG value multiply imputed at primary analysis time point based on the known assessments from the retrieved dropouts (i.e., subjects who discontinue before Week 23 but still have TG assessments at Week 23, 25, or 27), if there is a sufficient number of retrieved dropouts. The imputation model will include the following variables: TG values at baseline and postbaseline visits and the two randomization stratification factors. The multiple imputation will be stratified by treatment group. If there is not a sufficient number of retrieved dropouts, missing TG value at the primary time point will be imputed using a "wash-out" (Jump to Reference, J2R) multiple imputation approach. With the approach, subjects treated with olezarsen who discontinue study will have missing post-discontinuation TG values multiply imputed based on the fasting TG at baseline, two randomization stratification factors, and the imputation model for the placebo group. Subjects in the placebo group who discontinue the study will have missing post-discontinuation TG values multiply imputed based on fasting TG values at baseline and postbaseline visits from the placebo group.

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

The null hypothesis of the primary analysis is that the percent CFB to primary analysis time point in fasting TG is the same between each olezarsen and placebo treatment groups. The alternative hypothesis is that the percent CFB to primary analysis time point in fasting TG is different between each olezarsen and placebo treatment groups.

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

During the database lock cleaning process, redacted source documentation may need to be shared securely with the site Clinical Research Associate for source data verification procedures. The following sensitivity analyses of the primary endpoint will be conducted to assess the robustness of the primary analysis result, and details of the analyses will be outlined in the SAP:

- The primary analysis described above will be repeated in the per-protocol set (PPS).
- The primary analysis will be repeated in the subset of FAS with no missing TG value at the baseline and primary analysis time point.
- Additional sensitivity analyses using controlled imputations (pattern mixture models) with ANCOVA will be conducted in the FAS to assess the robustness of the primary analysis results.
 - For subjects treated with olezarsen who discontinue the study due to adverse event (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 subjects. The CIR approach is detailed in ([Carpenter et al. 2013](#)). The assumption is when a subject discontinues treatment due to informative missing, from withdrawal onwards they would progress in the same way as the subjects in the placebo group. For subjects who discontinue due to other reasons and all subjects from the placebo group, their missing data will be treated as non-informative missing, and data will be multiply imputed based on the distribution of their own arm.

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

Analysis of Secondary Endpoints

- The percent change in fasting TG from baseline to Month 12 in the FAS will be analyzed in the same way as the primary analysis of the primary endpoint.
- The proportion of subjects who achieve $\geq 40\%$ reduction in fasting TG from baseline to the primary analysis time point in the FAS will be compared between each olezarsen treatment group and placebo group using a logistic regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and log-transformed baseline TG as a covariate. Missing TG values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. A sensitivity analysis will be conducted in the FAS, in which all subjects who have missing data and discontinue treatment before Week 23 will be considered as non-responders.
- The percent change in fasting ApoC-III, ApoB-48, and non-HDL-C from baseline to the primary analysis time point and Month 12 in the FAS will be analyzed in the same way as the primary analysis of the primary endpoint.
- The proportion of subjects who achieve fasting TG ≤ 880 mg/dL at the primary analysis time point will be analyzed in the same way as the proportion of subjects who achieve $\geq 40\%$ reduction in fasting TG. Missing values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. It will be conducted in the subset of FAS with baseline TG > 880 mg/dL. A sensitivity analysis will be conducted in the subset of

FAS with baseline TG >880 mg/dL, in which all subjects who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

- The following adjudicated AP event rates
 - During the treatment period (Week 1 through 53) in the subset of FAS with a prior history of pancreatitis within 10 years prior to screening
 - During the treatment period (Week 1 through 53) in the FAS
 - From Week 13 to 53 in the subset of FAS with a prior history of pancreatitis within 10 years prior to screening
 - From Week 13 to 53 in the FAS
 - During the treatment period (Week 1 through 53) in the subset of FAS with two or more events of adjudicated AP in 5 years prior to enrollment
 - From Week 13 to 53 in the subset of FAS with two or more events of adjudicated AP in 5 years prior to enrollment
- Will be compared between pooled olezarsen treatment group and placebo group using a Poisson regression model or negative binomial regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated AP events in 5 years prior to the enrollment as a covariate. The logarithm of time in year that each subject observed during the corresponding analysis period (Week 13 to 53 or Week 1 to 53/ET) will be used as an offset variable.
- The proportion of subjects who achieve $\geq 70\%$ reduction in fasting TG from baseline to the primary analysis time point in the FAS will be analyzed in the same way as the proportion of subjects who achieve $\geq 40\%$ reduction in fasting TG. Missing values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. A sensitivity analysis will be conducted in the FAS, in which all subjects who have missing data and discontinue treatment before Week 23 will be considered as non-responders.
- The proportion of subjects who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point will be analyzed in the same way as the proportion of subjects who achieve $\geq 40\%$ reduction in fasting TG. Missing values will be imputed using the same multiple imputation method as the primary analysis of the primary endpoint. It will be conducted in the subset of FAS with baseline TG >500 mg/dL. A sensitivity analysis will be conducted in the subset of FAS with baseline TG >500 mg/dL, in which all subjects who have missing data and discontinue treatment before Week 23 will be considered as non-responders.

15.2. Trial ISIS 678354-CS8

The following is the Applicant's protocol synopsis of Trial ISIS 678354-CS8 from protocol amendment 2 (March 22, 2023), which was the final version of the protocol prior to the data cutoff.

Title

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

Landmark Dates

- First subject enrolled: June 1, 2022
- First subject dosed: June 1, 2022
- Last subject enrolled September 19, 2022
- Last subject, last dose: August 22, 2023
- Last subject, last visit: January 17, 2023
- Data cutoff: September 15, 2023
- Database Lock: October 20, 2023

Objectives

Primary

- To evaluate the effect of olezarsen on percent change in fasting TG levels as 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 ApoC-III, VLDL-C, remnant cholesterol, non-HDL-C, HDL-C, TC, ApoB, LDL-C, and ApoA-1
- Adjudicated AP event rate in patients with two or more events of AP pancreatitis in 5 years prior to enrollment
- Adjudicated AP event rate

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 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 Q4W 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 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. $\geq$ 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.

Population

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 $\geq$ 18 years at the time of informed consent
3. Fall into at least one of the following groups (a or b):

HTG with fasting TG $\geq$ 150 mg/dL (1.69 mmol/L) and <500 mg/dL (5.65 mmol/L) with either

Clinical diagnosis of atherosclerotic cardiovascular disease (ASCVD) defined as documented coronary artery disease, cerebrovascular disease, or peripheral artery disease or

At increased risk for ASCVD defined as:

1. Type 2 Diabetes mellitus, or
2. Two (2) or more of the following CV risk enhancing factors:
3. Men $\geq$ 55 years of age or women $\geq$ 65 years of age
4. Women with a history of preeclampsia, or premature menopause (before the age of 40 years)
5. Family history of premature ASCVD (before the age of 55 years for males, or before the age of 65 years for females)
6. Current tobacco use (5 cigarettes/day or more for at least 1 year)
7. Metabolic syndrome
8. Hypertension requiring antihypertensive treatment
9. Chronic kidney disease stage 3 or (eGFR 30-59 mL/min/m²)
10. LDL-C $\geq$ 160 mg/dL
11. LDL-C $\geq$ 100 mg/dL on therapy to lower LDL-C
12. Elevated high-sensitivity C-reactive protein ($\geq$ 2.0 mg/L)
13. Elevated lipoprotein (a) ($\geq$ 50 mg/dL or 125 nmol/L)
14. Ankle brachial index <0.9 in asymptomatic patients
15. Coronary artery calcium score $\geq$ 100

sHTG with fasting TG $\geq$ 500 mg/dL (5.65 mmol/L)

4. Patients should be on standard of care lipid-lowering medications per local guidelines. 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 OTC omega-3 fatty acids should make every effort to remain on the same brand through the end of the study.

Key Exclusion Criteria

1. Diabetes with any of the following:
 - Newly diagnosed within 12 weeks of screening
 - HbA1c $\geq 9.5\%$ at screening
 - Change in basal insulin regimen $>20\%$ within 3 months prior to screening
 - 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/ transient ischemic attack within 6 months prior to screening
3. Major surgery, peripheral revascularization, or non-urgent percutaneous coronary intervention 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

Sample Size

Approximately 152 subjects

Treatments

- Cohort A: Subjects will be randomized 3:1 to receive 50 mg olezarsen or matching volume of placebo SC Q4W for Weeks 1-49. Administered SC 0.5 mL volume
- Cohort B: Subjects will be randomized 3:1 to receive 80 mg olezarsen or matching volume of placebo SC Q4W for Weeks 1-49. Administered SC 0.8 mL volume

Endpoints

Primary

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

Secondary

- Percent change in fasting TG from baseline at Month 12 (average of Weeks 51 and 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 Months 6 and 12 compared to placebo

- Adjudicated AP event rate during the treatment period compared to placebo in patients with two or more events of adjudicated AP in 5 years prior to enrollment
- Adjudicated AP event rate during the treatment period compared to placebo

Procedures and Assessments

Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, olezarsen plasma trough concentrations, ADA testing, ECGs, and PRO assessments will be performed according to the schedule of procedures in [Table 124](#) below.

Table 124. Schedule of Procedures, Trial CS8

Study Week	Screening ^A		Treatment Period																Follow up Period		
	Run-in -4 to -2	Qual ^M -2 to -1	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
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
Adverse Events	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
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					

(Table 124 continued)

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/mm³ 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

Source: Trial CS8 CSR

Abbreviations: ADA, antidrug antibody; AE, adverse event; aPTT, activated partial thromboplastin time; CSR, clinical study report; ECG, electrocardiogram; ET, early termination; ET-L, early termination-landmark; FSH, follicle stimulating hormone; HbA1c, hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; INR, international normalized ratio; PK, pharmacokinetics; PLT, platelet; PT, prothrombin time; Qual, quality; SC, subcutaneous; TSH, thyroid stimulating hormone; Tx, treatment; UACR, urine albumin-to-creatinine ratio; UPCr, urine protein-to-creatinine ratio

Statistical Plan

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 group, no change in the placebo patients, and a common 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.

Analysis of the Primary Endpoint

The primary analysis of the primary endpoint is to compare the percent CFB 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 postbaseline visit and the multiple imputation will be stratified by treatment group ([Schafer 1997](#); [Schafer 1999](#)).

The Markov chain Monte Carlo 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 postbaseline 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 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 assumption in the primary analysis.
 - Patients with missing TG value at Month 6 will be imputed using a PMM. 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 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 postbaseline 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 postbaseline 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 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 myocardial infarction method as the primary analysis. Baseline and postbaseline 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.

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 $\geq$ 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 AP event rates in the subset of FAS with two or more events of adjudicated AP 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 AP 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.

15.3. Trial ISIS 678354–CS13

The following is the Applicant's protocol synopsis of Trial ISIS 678354-CS13 from protocol amendment 4 (March 3, 2023), which was the final version of the protocol prior to the data cutoff.

Title

An Open-Label Extension Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)

Landmark Dates

- First subject enrolled and dosed: December 20, 2021
- Last Subject, Last Visit: Not applicable, study ongoing
- Data Cutoff Date: August 5, 2023 (interim)
- Database Lock Date: September 21, 2023 (interim)

Objectives

Primary

- To evaluate the safety and tolerability of olezarsen

Study Design

This is a multi-center OLE study of FCS patients rolling-over from ISIS 678354-CS3 (the index study). Patient eligibility should be determined during the Qualification Period within 31 days prior to study entry. Patients will receive olezarsen at the dose of 80 mg Q4W (or 50 mg every-4-weeks if their dose was permanently reduced from 80 mg to 50 mg (olezarsen or placebo) in the index study) during Weeks 1 through 153 of a 157-week Treatment Period, followed by a 13-week post-treatment follow-up period. The 80 mg dose may be adjusted to 50 mg Q4W

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(temporarily or permanently) for tolerability or safety reasons following consultation with the Sponsor Medical Monitor. Dietary counseling will be reinforced at intervals throughout the treatment and post-treatment follow-up periods.

Population

Key Inclusion Criteria

- Satisfactory completion of the ISIS 678354-CS3 index study (last dose as scheduled at Week 49) with an acceptable safety profile, per investigator judgement.

Key Exclusion Criteria

- Have any new condition or worsening of existing condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study, including need for treatment with medications disallowed in the index study (ISIS 678354-CS3).

Treatments

For each individual patient who receives 80 mg of olezarsen, it will be administered SC either as a single 0.8 mL injection using vial, or 80 mg autoinjector every-4-weeks for a total of 39 doses (Weeks 1 to 153). For each individual patient who has dose reduced to 50 mg of olezarsen, it will be administered SC either as a single 0.5 mL injection using vial, or using a 50 mg autoinjector every-4-weeks.

Endpoints

Safety endpoints include a proportion of patients who show the following changes from baseline to Week 53, Week 105, and Week 157:*

- Decrease in platelet count by >30%
- Decrease in platelet count by >50%
- Platelet count value <50,000 mm³
- Major bleeding events
- Clinically relevant non-major bleeding events
- Decrease in eGFR by >30%
- Decrease in eGFR by >50%
- UPCR $\geq$ 1000 mg/g
- UACR $\geq$ 500 mg/g
- ALT or AST $>5 \times$ ULN
- Total bilirubin >2.0 mg/dL
- ALT or AST $>3 \times$ ULN and total bilirubin $>2 \times$ ULN

* *Lab values based on confirmed results.*

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In addition, rate of MACE will be summarized. Tolerability assessments include AEs, clinical laboratory tests, and use of concomitant medications.

Other endpoints included changes in lipid parameters such as TG and ApoB48 (average changes and categorical changes) and rate of pancreatitis events.

Procedures and Assessments

Table 125. Schedule of Procedures, Trial CS13

Appendix A Schedule of Procedures (Year 1)

Study Week ^γ	Qual ^A	Treatment Period																
		1	5 ^K	9 ^K	13 ^K	17 ^K	21 ^K	23/ET-L1 ^{K,M}	25/ET-L2 ^{K,M}	27/ET-L3 ^{K,M}	29 ^K	33 ^K	37 ^K	41 ^K	45 ^K	49 ^K	51/ET-L4 ^{K,M}	53/ET-L5 ^{K,M} or TxET ^K
Study Day	-31 to -1	1 ^B	29	57	85	113	141	155	169	183	197	225	253	281	309	337	351	365
Visit Window ± Days	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Informed Consent	X																	
Inclusion/Exclusion	X																	
Body Weight	X	X							X									X
Vital Signs	X	X			X				X				X					X
Signs/symptoms of pancreatitis (per Section 6.2.2)	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X
Physical Examination	X	X							X									X
12-lead ECG (triplicate)		X							X									X
Pregnancy Test ^C	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X
Extended Urinalysis ^D	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X
Chemistry Panel ^{E, F}	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X
Hematology ^E	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X
Coagulation (aPTT, PT, INR)		X							X									X
Lipid Panel ^F		X	X	X	X	X	X	X	X	X	X		X		X		X	X
HbA1c		X							X									X
hsCRP		X							X									X
ADA ^G		X	X		X				X				X					X
Plasma PK - ISIS 678354 ^G		X	X		X				X				X					X
Archived Serum & Plasma Samples ^H		X			X			X	X	X							X	X
Assessment of ER Visits, Hospitalization, and Inpatient Days		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit Interview (selected sites)		As scheduled after Week 13 visit																
AEs	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
Diet/Alcohol Counseling ^I		X	X		X		X		X		X		X		X			X

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Study Week	Qual ^A	Treatment Period																
	-4 to 1	1	5 ^K	9 ^K	13 ^K	17 ^K	21 ^K	23/ET-L1 ^{K,M}	25/ET-L2 ^{K,M}	27/ET-L3 ^{K,M}	29 ^K	33 ^K	37 ^K	41 ^K	45 ^K	49 ^K	51/ET-L4 ^{K,M}	53/ET-L5 ^{K,M} or TxET ^K
Study Day	-31 to -1	1 ^B	29	57	85	113	141	155	169	183	197	225	253	281	309	337	351	365
Visit Window ± Days	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Study Drug: SC Injection ^J		X	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 Patient eligibility for the study should be determined within 31 days prior to study entry. A Qualification Period longer than 31 days may be considered after discussion with the Sponsor Medical Monitor, but the intention is to continue treatment (from the index study) without any interruption. Safety clinical laboratory parameters and assessments from the index study may be used for determination of eligibility for this ISIS 678354-CS13 study if they were obtained within the Qualification Period (i.e., 31 days prior to enrollment in the study or longer if approved by the Sponsor Medical Monitor)
- ^B Study Day 1 can be conducted on the same day as the index study (ISIS 678354-CS3) Week 53 visit and safety, clinical laboratory parameters and assessments from this index Study Week 53 visit may be used for this ISIS 678354-CS13 study. All procedures at Day 1 and all other study visits are to be completed prior to ISIS 678354 administration. Study Day 1 must occur within 17 weeks of the last administration of ISIS 678354 in ISIS 678354-CS3 (i.e., CS3 Study Week 49)
- ^C Urine pregnancy test for women who are not surgically sterile or postmenopausal
- ^D 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
- ^E If the PLT, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 3 days and not later than 7 days). All 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/mm³ should be reported in an expedited fashion to the Sponsor
- ^F Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours
- ^G Refer to [Appendix C](#) for PK/ADA sampling schedule
- ^H Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report
- ^I Recommended time points for qualified site personnel to reinforce compliance to diet and alcohol restrictions
- ^J Patients to receive 80-mg ISIS 678354 every 4 weeks for Weeks 1-49, except for patients randomized to 80 mg every 4 weeks dose (ISIS 678354 or placebo) in the index study who had subsequently dose reduced permanently to 50 mg every 4 weeks: these patients will receive 50 mg ISIS 678354 every 4 weeks in this study
- ^K Assessments and procedures to be conducted by either the Study Center or by a Home Healthcare service (if available) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional
- ^M Landmark visit. For early termination landmark (ET-L) visits: Week 23 is ET-L1, Week 25 is ET-L2, Week 27 is ET-L3, Week 51 is ET-L4, and Week 53 is ET-L5

Study Week	Treatment Period														103/ET-L6 ^{K,M}	105/ET-L7 ^{K,M} or TxET ^K
	57 ^K	61 ^K	65 ^K	69 ^K	73 ^K	77 ^K	81 ^K	85 ^K	89 ^K	93 ^K	97 ^K	101 ^K				
Study Day	393	421	449	477	505	533	561	589	617	645	673	701	715	729		
Visit Window ± Days	5	5	5	5	5	5	5	5	5	5	5	5	5	5		
Body Weight							X							X		
Vital Signs							X							X		
Signs/Symptoms of Pancreatitis (per Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	X		X		
Physical Examination							X							X		
12-lead ECG (triplicate)							X							X		
Pregnancy Test ^C	X	X	X	X	X	X	X	X	X	X	X	X		X		
Extended Urinalysis ^D	X		X		X		X		X		X			X		
Chemistry Panel ^{E, F}	X		X		X		X		X		X			X		
Hematology ^E	X		X		X		X		X		X			X		
Coagulation (aPTT, PT, INR)							X							X		
Lipid Panel ^F	X		X		X		X		X		X		X	X		
HbA1c							X							X		
hsCRP							X							X		
ADA ^G							X							X		
Archived Serum & Plasma Samples ^H							X						X	X		
Assessment of ER Visits, Hospitalization, and Inpatient Days	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AEs	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		
Diet/Alcohol Counseling ^I	X		X		X		X			X				X		
Study Drug: SC Injection ^J	X	X	X	X	X	X	X	X	X	X	X	X		X		

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

Legend

- ^C Urine pregnancy test for women who are not surgically sterile or postmenopausal.
- ^D 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.
- ^E If the PLT, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 3 days and not later than 7 days). All 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/mm³ should be reported in an expedited fashion to the Sponsor.
- ^F Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours.
- ^G Refer to [Appendix C](#) for ADA sampling schedule.
- ^H Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report.
- ^I Recommended time points for qualified site personnel to reinforce compliance to diet and alcohol restrictions.
- ^J Patients to receive 80-mg ISIS 678354 every 4 weeks for Weeks 57-105, except for patients randomized to 80 mg every 4 weeks dose (ISIS 678354 or placebo) in the index study who had subsequently dose reduced permanently to 50 mg every 4 weeks: these patients will receive 50 mg ISIS 678354 every 4 weeks in this study.
- ^K Assessments and procedures to be conducted by either the Study Center or by a Home Healthcare service (if available) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional.
- ^M Landmark visit. For early termination landmark (ET-L) visits: Week 103 is ET-L6, Week 105 is ET-L7.

Study Week	Treatment Period													Follow-up Period			
	109 ^K	113 ^K	117 ^K	121 ^K	125 ^K	129 ^K	133 ^K	137 ^K	141 ^K	145 ^K	149 ^K	153 ^K	155/ET-L8 ^{K,M}	157/ET-L9 ^{K,M} or Tx ET ^K	4 ^{K,L}	8 ^{K,L}	13 ^{K,L} or Post-Tx ET ^K
Study Day	757	785	813	841	869	897	925	953	981	1009	1037	1065	1079	1093	28 ^I	56 ^I	91 ^I
Visit Window ± Days	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Body Weight						X								X			X
Vital Signs						X								X			X
Signs/Symptoms of Pancreatitis (per Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination														X			X
12-lead ECG (triplicate)														X			X
Pregnancy Test ^C	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Extended Urinalysis ^D			X			X			X			X		X			X
Chemistry Panel ^{E,F}			X			X			X			X		X			X
Hematology ^E			X			X			X			X		X			X
Coagulation (aPTT, PT, INR)						X								X			
Lipid Panel ^F			X			X			X				X	X	X	X	X
HbA1c						X								X			X
hsCRP						X								X			X
ADA ^G						X								X			X
Plasma PK - ISIS 678354 ^G															X	X	X
Archived Serum & Plasma Samples ^H						X							X	X			X
Assessment of ER Visits, Hospitalization, and Inpatient Days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	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
Diet/Alcohol Counseling ^I			X			X			X			X		X		X	
Study Drug: SC Injection ^J	X	X	X	X	X	X	X	X	X	X	X	X					

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

Legend

- ^C Urine pregnancy test for women who are not surgically sterile or postmenopausal.
- ^D 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.
- ^E If the PLT, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 3 days and not later than 7 days). All 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/mm³ should be reported in an expedited fashion to the Sponsor.
- ^F Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours.
- ^G Refer to [Appendix C](#) for PK/ADA sampling schedule.
- ^H Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report.
- ^I Recommended time points for qualified site personnel to reinforce compliance to diet and alcohol restrictions.
- ^J Patients to receive 80-mg ISIS 678354 every 4 weeks for Weeks 109-157, except for patients randomized to 80 mg every 4 weeks dose (ISIS 678354 or placebo) in the index study who had subsequently dose reduced permanently to 50 mg every 4 weeks: these patients will receive 50 mg ISIS 678354 every 4 weeks in this study.
- ^K Assessments and procedures to be conducted by either the Study Center or by a Home Healthcare service (if available) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional.
- ^L Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (4 weeks) post-last dose.
- ^M Landmark visit. For early termination landmark (ET-L) visits: Week 155 is ET-L8, Week 157 is ET-L9.

Source: CS13 CSR

Abbreviations: ADA, antidrug antibody; AE, adverse event; aPTT, activated partial thromboplastin time; ECG, electrocardiogram; CSR, clinical study report; ET, early termination; ET-L, early termination-landmark; FSH, follicle stimulating hormone; HbA1c, hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; INR, international normalized ratio; PK, pharmacokinetics; PLT, platelet; PT, prothrombin time; Qual, quality; SC, subcutaneous; TSH, thyroid stimulating hormone; Tx, treatment; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

Statistical Plan

Treatment duration and amount of olezarsen received will be summarized by treatment group in the index study and overall. The proportion of patients who experience the events listed in the endpoints above from baseline to Week 53, 105, and 157 and during the study period will be tabulated by treatment group in the index study and overall.

For the lab events, the proportion of patients based on the confirmed results will also be tabulated.

Patient incidence rates of all AEs will be tabulated by MedDRA SOC and PT, and by treatment group in the index study and overall. Tables and/or narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All TEAEs, all TEAEs potentially related to olezarsen, all serious TEAEs, and all serious TEAEs potentially related to olezarsen will be summarized. Laboratory tests to ensure patient safety, including chemistry panel, complete blood count with differential, coagulation panel, etc., will be summarized by study visit for each treatment group in the index study and overall. These safety variables will also be presented as change and percent CFB over time, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group in the index study and overall.

The adjudicated MACE event rates will be summarized by the treatment group in index study and overall.

The safety data may also be summarized by the treatment group in the OLE study if supported by data.

The change and percent change in fasting TG and ApoB48 from baseline at Months 6, 12, 24 and 36, will be summarized by the treatment group in index study and overall.

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The Month 6 endpoint is defined as the average of Weeks 23, 25 and 27. The Month 12 endpoint is defined as the average of Weeks 51 and 53, the Month 24 endpoint is defined as average of Weeks 103 and 105, and the Month 36 endpoint is defined as average of Weeks 155 and 157.

The adjudicated AP event rates will be summarized by the treatment group in index study and overall. The efficacy data may also be summarized by the treatment group in the OLE study if supported by data.

15.4. Trial ISIS 678354-CS7

The following is the Applicant's protocol synopsis of Trial ISIS 678354-CS7 from protocol amendment 3 (February 9, 2023), which was the final version of the protocol prior to the data cutoff.

Title

An Open-Label Safety Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS) Previously Treated With Volanesorsen (ISIS 304801)

Landmark Dates

- First Subject Enrolled: March 22, 2022
- Last Subject Enrolled: February 28, 2023
- First Subject Dosed: March 24, 2022
- Last Subject, Last Visit: Ongoing
- Data Cutoff Date: May 31, 2023 (interim)
- Database Lock Date: July 31, 2023 (interim)

Objectives

Primary

To evaluate the safety and tolerability of olezarsen in subjects with FCS previously treated with volanesorsen

Secondary

To evaluate the PK and PD effects of olezarsen in subjects with FCS previously treated with volanesorsen

Study Design

This is a multi-center open-label safety study of FCS patients previously treated with volanesorsen (ISIS 304801) to guide the transition to olezarsen.

Following an up to 8-week screening period (including an up to 4-week run-in washout period for patients treated with volanesorsen within 4 weeks prior to screening, and a 4-week, but not

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less than, 2-week qualification period), patients (N= ~24) will receive olezarsen at least 6 weeks after their last dose of volanesorsen at the dose of 80 mg Q4W during Weeks 1 to 153 of the 157-week treatment period, followed by a 13-week post-treatment follow-up period. This dose may be adjusted to 50 mg Q4W due to tolerability or safety reasons at any point during the study following consultation with the Sponsor Medical Monitor.

Dietary counseling will be reinforced at intervals throughout the treatment and post-treatment evaluation periods.

An independent Data Safety Monitoring Board will periodically review the data collected.

An independent Adjudication Committee will adjudicate all AP events on study.

Population

Key Inclusion Criteria

1. Patients with FCS (clinical or genetic diagnosis) currently on or previously treated with volanesorsen (ISIS 304801)

Study participants in countries where Waylivra® is commercially approved and available for the patients should not be deprived of the treatment option with Waylivra®. Participation in this study for such patients will only be allowed when Waylivra® was discontinued due to AEs.

Key Exclusion Criteria

1. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 4 weeks of screening, or 5 half-lives of investigational agent, whichever is longer
2. Have any other conditions including significant medical history which, in the opinion of the investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

Treatments

For each individual patient who receives 80 mg of olezarsen, it will be administered SC either as a single 0.8 mL injection using vial, or 80 mg autoinjector, Q4W for a total of 39 doses (Week 1 to 153).

For each individual patient who has dose reduced to 50 mg of olezarsen it will be administered SC either as a single 0.5 mL injection using vial, or a single (b) (4) mL injection using a 50 mg autoinjector, Q4W

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Endpoints

Safety endpoints include a proportion of patients who show the following changes from baseline to Week 53, Week 105, and Week 157:*

- Decrease in platelet count by >30%
- Decrease in platelet count by >50%
- Platelet count value <50,000 mm³
- Major bleeding events
- Clinically relevant non-major bleeding events
- Decrease in eGFR by >30%
- Decrease in eGFR by >50%
- UPCR $\geq$ 1000 mg/g
- UACR $\geq$ 500 mg/g
- ALT or AST $>5 \times$ ULN
- Total bilirubin >2.0 mg/dL
- ALT or AST $>3 \times$ ULN and total bilirubin $>2 \times$ ULN

* *Lab values based on confirmed results.*

Tolerability assessments include AEs clinical laboratory tests, and use of concomitant medications.

Other endpoints included changes in lipid parameters such as TG and ApoB48 (average changes and categorical changes) and rate of pancreatitis events.

Procedures and Assessments

Table 126. Schedule of Procedures, Trial CS7

Appendix A Schedule of Procedures (Year 1)

Study Week	Screening Period		Treatment Period													
	Run-in Washout	Qualification	1	5 ^M	9 ^M	13 ^M	17 ^M	21 ^M	25 ^M	29 ^M	33 ^M	37 ^M	41 ^M	45 ^M	49 ^M	53/L1 ^{M,N}
Study Day	-57 to -29	-28 to -1	1 ^A	29	57	85	113	141	169	197	225	253	281	309	337	365
Visit and Testing Window ± Days			0 ^A	3	3	3	3	3	3	3	3	3	3	3	3	3
Informed Consent	X															
Medical History	X															
FSH ^B		X														
Inclusion/Exclusion Criteria	X		X													
Body Weight and Height ^C		X							X							X
Vital Signs		X	X			X			X			X				X
Physical Examination		X	X						X							X
12-lead ECG (triplicate)		X	X						X							X
Pregnancy Test ^D		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Extended Urinalysis ^E		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry ^{F,G}		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology ^F		X	EVERY-14-DAYS (± 3 days)				X	X	X	X	X	X	X	X	X	X
Coagulation (aPTT, PT, INR)		X	X						X							X
Lipid Panel ^{F,G}		X	X	X	X	X	X	X	X	X		X		X	X	X
HbA1c		X	X						X							X
hsCRP		X	X						X							X
PLT Panel ^H			X													
Anti-drug Antibody (ADA) ^I			X	X		X			X							X
Plasma PK - ISIS 678354 ^J			X	X		X			X							X
Archived Serum & Plasma Samples ^J			X			X			X					X		X
Adverse Events	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
Diet/Alcohol Counseling ^K		X	X			X			X			X			X	X
ISIS 678354 Administration ^L : SC Injection			X	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 (Year 1)

- ^A 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 ISIS 678354 dose. The first dose of ISIS 678354 must be at least 6 weeks after the patient's last dose of volanesorsen
- ^B For confirmation of menopause at Screening per inclusion criteria
- ^C Height only required at Screening
- ^D 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
- ^E 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
- ^F 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/mm³ should be reported in an expedited fashion to the Sponsor
- ^G Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. Fasting is not required for confirmatory tests, repeated uninterpretable, or missing tests, or tests taken for safety reasons
- ^H Refer to Table 3 in Section 8.5.3
- ^I Refer to Appendix C for PK/ADA sampling schedule
- ^J Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report
- ^K Recommended timepoints for qualified site personnel to reinforce compliance to diet and alcohol restrictions
- ^L ISIS 678354 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) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional
- ^N Landmark visit (L)

Appendix A Schedule of Procedures (Year 2)

	Treatment Period													
Study Week	57 ^M	61 ^M	65 ^M	69 ^M	73 ^M	77 ^M	81 ^M	85 ^M	89 ^M	93 ^M	97 ^M	101 ^M	105/L2 ^{M,N}	
Study Day	393	421	449	477	505	533	561	589	617	645	673	701	729	
Visit Window ± Days	5	5	5	5	5	5	5	5	5	5	5	5	5	
Body Weight							X						X	
Vital Signs							X						X	
Physical Examination							X						X	
12-lead ECG (triplicate)							X						X	
Pregnancy Test ^D	X	X	X	X	X	X	X	X	X	X	X	X	X	
Extended Urinalysis ^E	X		X		X		X		X		X		X	
Chemistry Panel ^{F,G}	X		X		X		X		X		X		X	
Hematology ^F	X		X		X		X		X		X		X	
Coagulation (aPTT, PT, INR)							X						X	
Lipid Panel ^{F,G}	X		X		X		X		X		X		X	
HbA1c							X						X	
hsCRP							X						X	
PLT Panel ^H														
ADA ^I							X						X	
Archived Serum & Plasma Samples ^J							X						X	
Adverse Events	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	
Diet/Alcohol Counseling ^K			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 (Year 2)

- D 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
- E 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
- F 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/mm³ should be reported in an expedited fashion to the Sponsor
- G Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. Fasting is not required for confirmatory tests, repeated uninterpretable, or missing tests, or tests taken for safety reasons
- H Refer to Table 3 in Section 8.5.3
- I Refer to Appendix C for PK/ADA sampling schedule
- J Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report
- K Recommended timepoints for qualified site personnel to reinforce compliance to diet and alcohol restrictions
- L ISIS 678354 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) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional
- N Landmark visit (L)

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Study Week	Treatment Period													Post-Treatment Follow-up Period		
	109 ^M	113 ^M	117 ^M	121 ^M	125 ^M	129 ^M	133 ^M	137 ^M	141 ^M	145 ^M	149 ^M	153 ^M	157/L3 or ET-Tx ^{M,N}	4 ^{M,O}	8 ^{M,O}	13 ^{M,O} or Post-Tx ET ^{M,O}
Study Day	757	785	813	841	869	897	925	953	981	1009	1037	1065	1093	28 ^I	56 ^I	91 ^I
Visit Window ± Days	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Body Weight					X								X			X
Vital Signs					X								X			X
Physical Examination													X			X
12-lead ECG (triplicate)													X			X
Pregnancy Test ^D	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Extended Urinalysis ^E		X			X			X			X		X			X
Chemistry Panel ^{F,G}		X			X			X			X		X			X
Hematology ^F		X			X			X			X		X			X
Coagulation (aPTT, PT, INR)					X								X			
Lipid Panel ^{F,G}		X			X			X					X	X	X	X
HbA1c					X								X			X
hsCRP					X								X			X
PLT Panel ^H																
ADA ^I					X								X			X
Plasma PK - ISIS 678354 ^L														X	X	X
Archived Serum & Plasma Samples ^J					X								X			X
Adverse Events	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
Diet/Alcohol Counseling ^K		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 (Year 3)

- D 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
- E 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
- F 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/mm3 should be reported in an expedited fashion to the Sponsor
- G Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. Fasting is not required for confirmatory tests, repeated uninterpretable, or missing tests, or tests taken for safety reasons
- H Refer to Table 3 in Section 8.5.3
- I Refer to Appendix C for PK/ADA sampling schedule
- J Serum and plasma archive samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until at least completion of the final study report
- K Recommended timepoints for qualified site personnel to reinforce compliance to diet and alcohol restrictions
- L ISIS 678354 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) as arranged by the Study Center personnel. Physical Exam will be Body Assessment if conducted by a Home Healthcare professional
- N Landmark visit (L) or early termination visit (ET). ET-Tx – early termination from Treatment Period visit (Week 157); Post-Tx ET – early termination from the Post-Treatment Follow-up visit (Week 13 of the Post-Treatment Follow-up Period)
- O Weeks/days from end of treatment period. End of treatment period is defined as 1 dosing interval (4 weeks) post-last dose

Source: CS7 CSR

Abbreviations: ADA, antidrug antibody; AE, adverse event; aPTT, activated partial thromboplastin time; CSR, clinical study report; ECG, electrocardiogram; ET, early termination; ET-L, early termination-landmark; FSH, follicle stimulating hormone; HbA1c, hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; INR, international normalized ratio; PK, pharmacokinetics; PLT, platelet; PT, prothrombin time; Qual, quality; SC, subcutaneous; TSH, thyroid stimulating hormone; Tx, treatment; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

Statistical Plan

Treatment duration and amount of olezarsen received will be summarized by treatment group in the index study and overall. The proportion of patients who experience the events listed in the endpoints above from baseline to Week 53, 105, and 157 and during the study period will be tabulated by treatment group in the index study and overall.

For the lab events, the proportion of patients based on the confirmed results will also be tabulated.

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Patient incidence rates of all AEs will be tabulated by MedDRA system organ class (SOC) and PT, and by treatment group in the index study and overall. Tables and/or narratives of treatment emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All TEAEs, all TEAEs potentially related to olezarsen, all serious TEAEs, and all serious TEAEs potentially related to olezarsen will be summarized. Laboratory tests to ensure patient safety, including chemistry panel, complete blood count with differential, coagulation panel, etc., will be summarized by study visit for each treatment group in the index study and overall. These safety variables will also be presented as change and percent CFB over time, as appropriate.

Vital sign and ECG measures will be tabulated.

The adjudicated MACE event rates will be summarized by the treatment group in index study and overall.

The change and percent change in fasting TG and other PD endpoints (ApoC-III, ApoB, VLDL-C, etc.) from baseline at Week 53, Week 105, and Week 157 will be summarized.

The adjudicated AP event rates (Week 1 through Weeks: 53, 105, and 157) will be summarized.

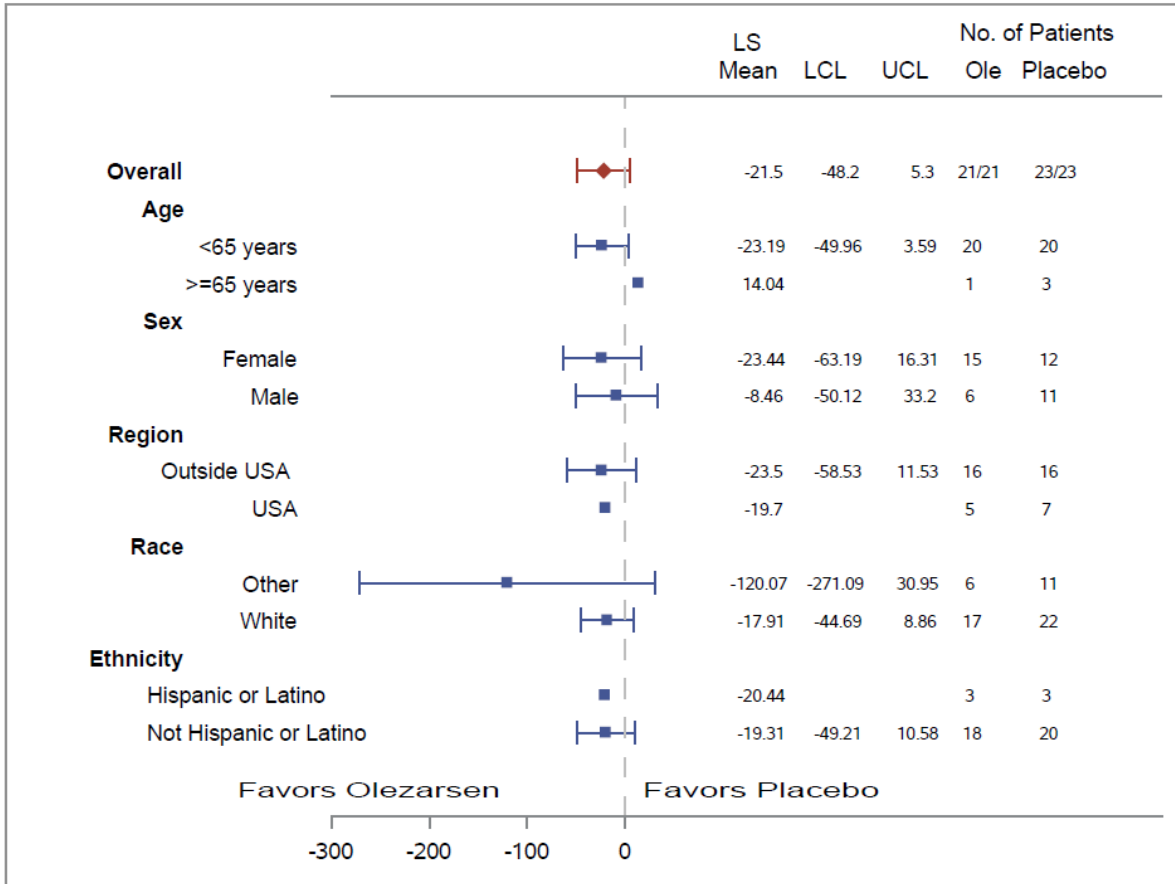
16. Efficacy

16.1. Trial ISIS 678354-CS3, Subgroup Analyses

Subgroup Analyses of the Primary Endpoint for Study CS3

Subgroup analyses were performed on the primary endpoint, fasting TG by age group (<65 years, ≥65 years), sex (female, male), region (outside of USA, USA), race (Asian, Native Hawaiian or Other Pacific Islander, Other, White), and ethnicity (Hispanic or Latino, Not Hispanic or Latino). [Figure 67](#) shows the subgroup analysis results for olezarsen 50 mg vs. placebo, and [Figure 68](#) shows the subgroup analysis results for olezarsen 80 mg vs. placebo. The subgroup analyses were performed using the FAS population. This study was conducted in mainly White, females, <65 years of age, outside of the USA. Due to some very small patient subgroups, some estimates/95% CIs were not able to be calculated. The subgroup for race was combined to Other and White due to very few patients in the Asian, Native Hawaiian and Other Pacific Islander, and Other categories.

Figure 67. Subgroup Analysis: Fasting Triglycerides (mg/dL) at Month 6, Olezarsen 50 mg vs. Placebo, Trial CS3



Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt

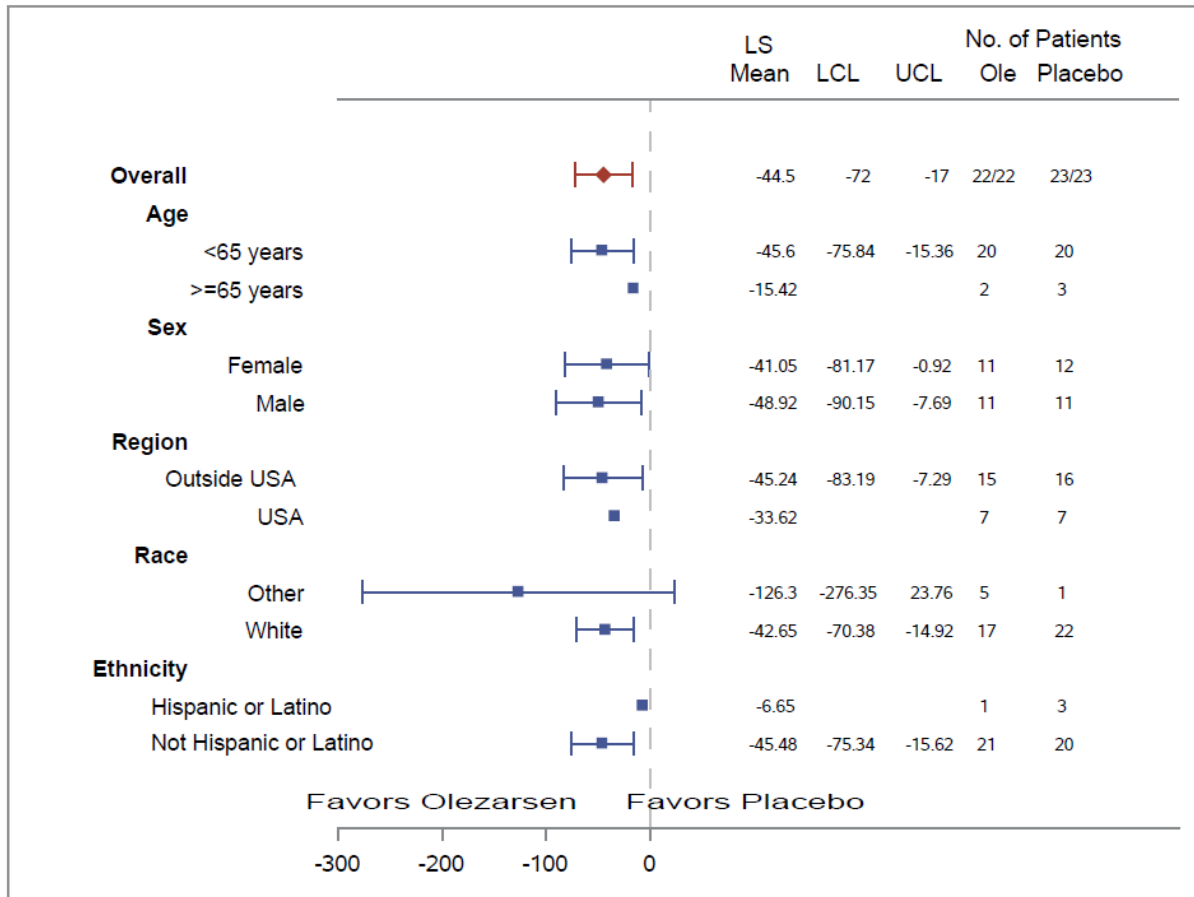
The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27.

Note: LS Means are from the analysis of covariance model with treatment (Olezarsen 50 mg, Placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline triglyceride as a covariate for each subgroup. Missing data was imputed using Washout imputation.

Other: Asian, Native Hawaiian and Other Pacific Islander, and Other

Abbreviations: CI, confidence interval; Ole, number of subjects in Olezarsen group; Placebo, number of subjects in Placebo group; LS Means, least squares means; LCL, lower confidence; UCL, upper confidence

Figure 68. Subgroup Analysis: Fasting Triglycerides (mg/dL) at Month 6, Olezarsen 80 mg vs. Placebo, Trial CS3



Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt
 The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27.
 Note: LS Means are from the analysis of covariance model with treatment (Olezarsen 50 mg, Placebo), the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline triglyceride as a covariate for each subgroup. Missing data was imputed using Washout imputation.
 Other: Asian, Native Hawaiian and Other Pacific Islander, and Other
 Abbreviations: CI, confidence interval; LCL, lower confidence; LS Means, least squares means; Ole, number of subjects in Olezarsen group; Placebo, number of subjects in Placebo group; UCL, upper confidence

There were likely some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derived shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a “weighted” average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior to derive shrinkage estimates for all subgroups (age, sex,

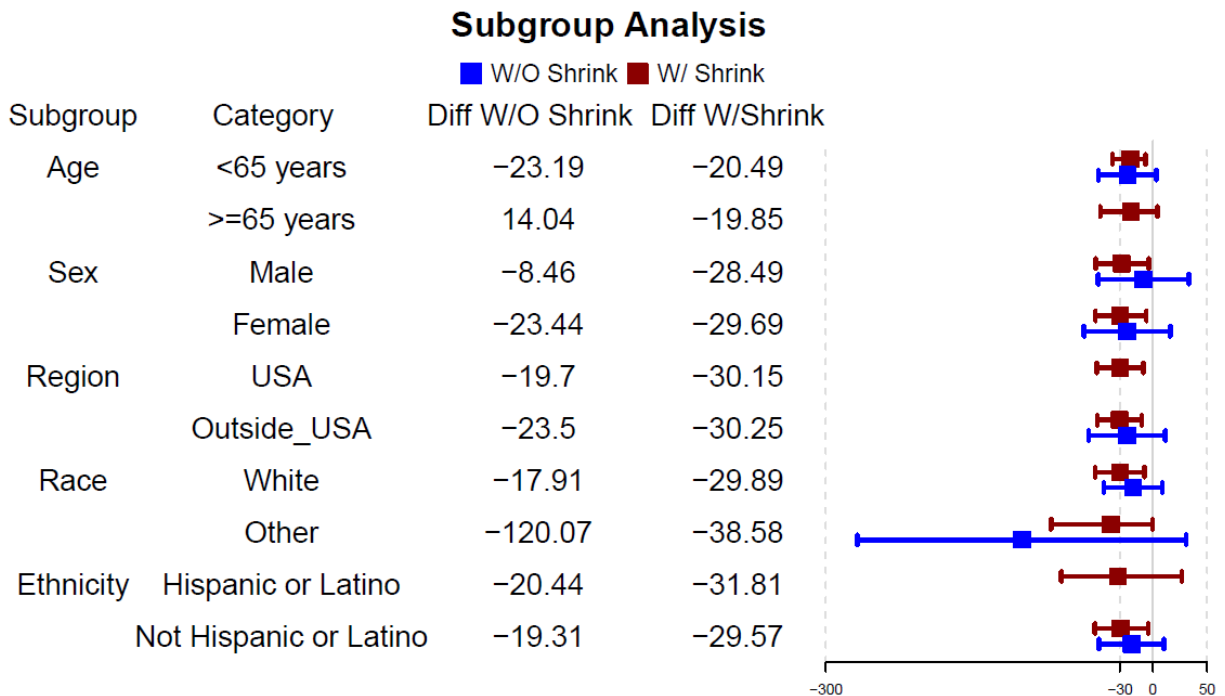
region, race, and ethnicity). The Bayesian hierarchical model assumptions for fasting TG at Month 6 are:

For $i = 1, 2, \dots$ Y_i represents the observed sample estimate of treatment effect in a subgroup level i , assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 140)$, $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$

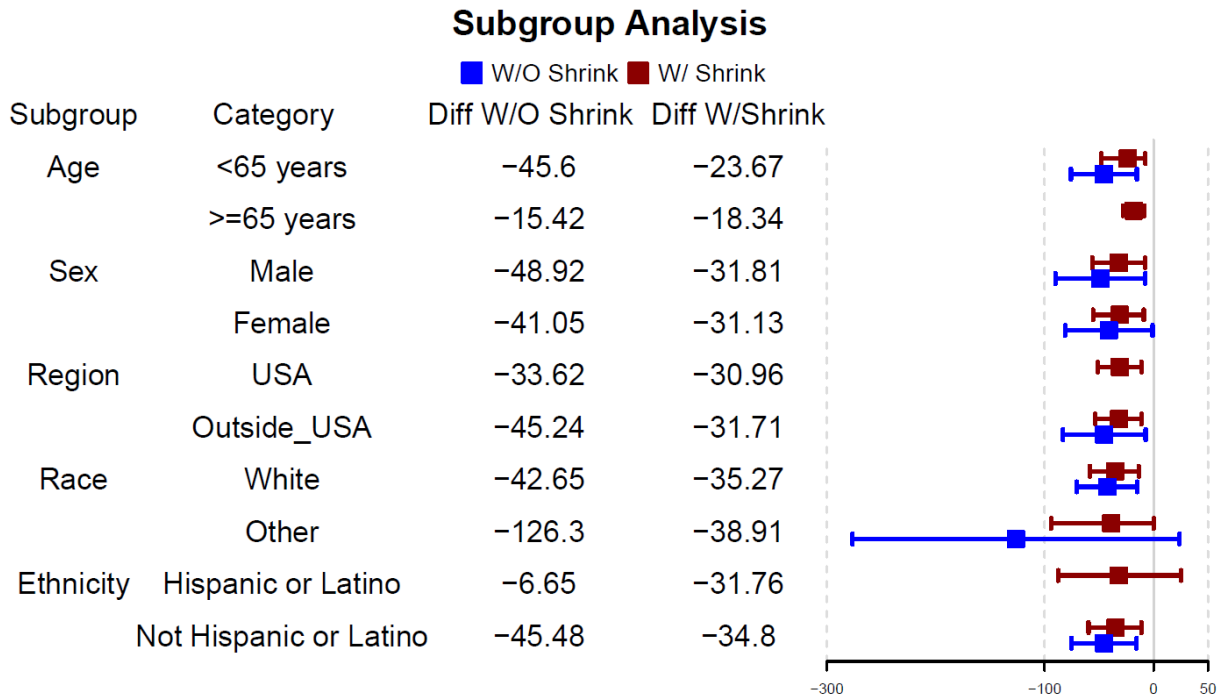
The variance should be selected relative to the residual standard deviation from the primary analysis model. In general, it should be 4 to 10 times of the residual SD. A flat prior with mean 0 and SD of 140 was chosen. This SD is 4 times the residual SD and so this assumption would not be influential. [Figure 69](#) for olezarsen 50 mg vs. placebo and [Figure 70](#) for olezarsen 80 mg vs. placebo compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of fasting TG at Month 6. The overall treatment effect for 50 mg was -21.5 (95% CI: -48.2, 5.3) and for 80 mg was -44.5 (95% CI: -72.0, -17.0). Subgroup analysis using Bayesian shrinkage estimate exhibits narrower CI, and the shrinkage subgroup estimate is closer to the overall mean.

Figure 69. Subgroup Shrinkage Analysis: Mean Fasting Triglycerides (mg/dL) at Month 6 Olezarsen 50 mg vs. Placebo, Trial CS3



Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt; Other:

**Figure 70. Subgroup Shrinkage Analysis: Mean Fasting Triglycerides (mg/dL) at Month 6
 Olezarsen 80 mg vs. Placebo, Trial CS3**



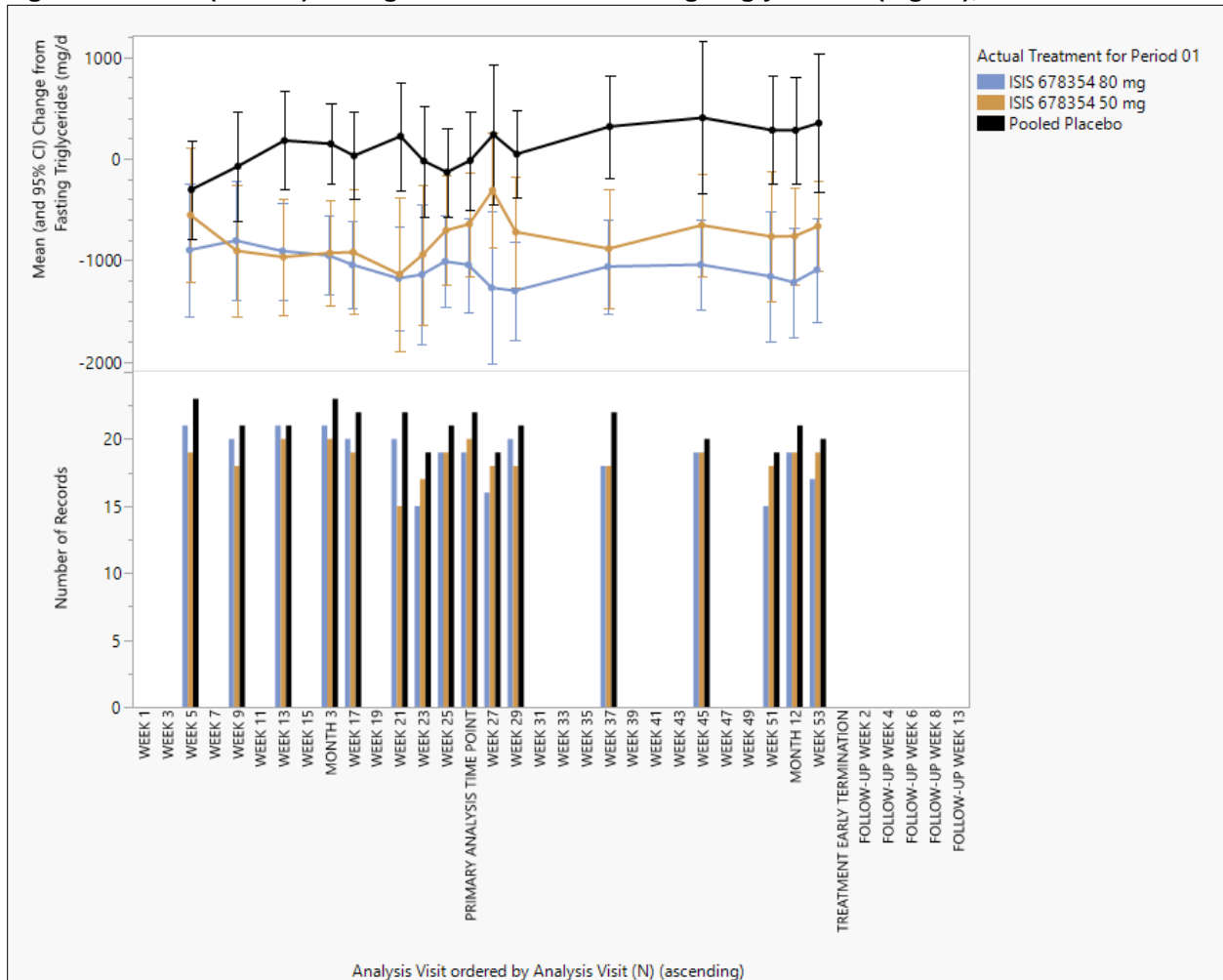
Source: Statistical Reviewer's Analysis; adsl.xpt, adefl.xpt

16.2. Trial ISIS 678354-CS3, Supportive Analyses

Additional supportive evidence of TG reduction observed with olezarsen 80 mg as compared to placebo are shown in the following tables and figures in several lipid and lipoprotein parameters.

[Figure 71](#) shows the mean (95% CI) change from baseline in TG over time. This figure demonstrates that the reduction in TG with olezarsen 80 mg showed persistence over time until the end of the trial.

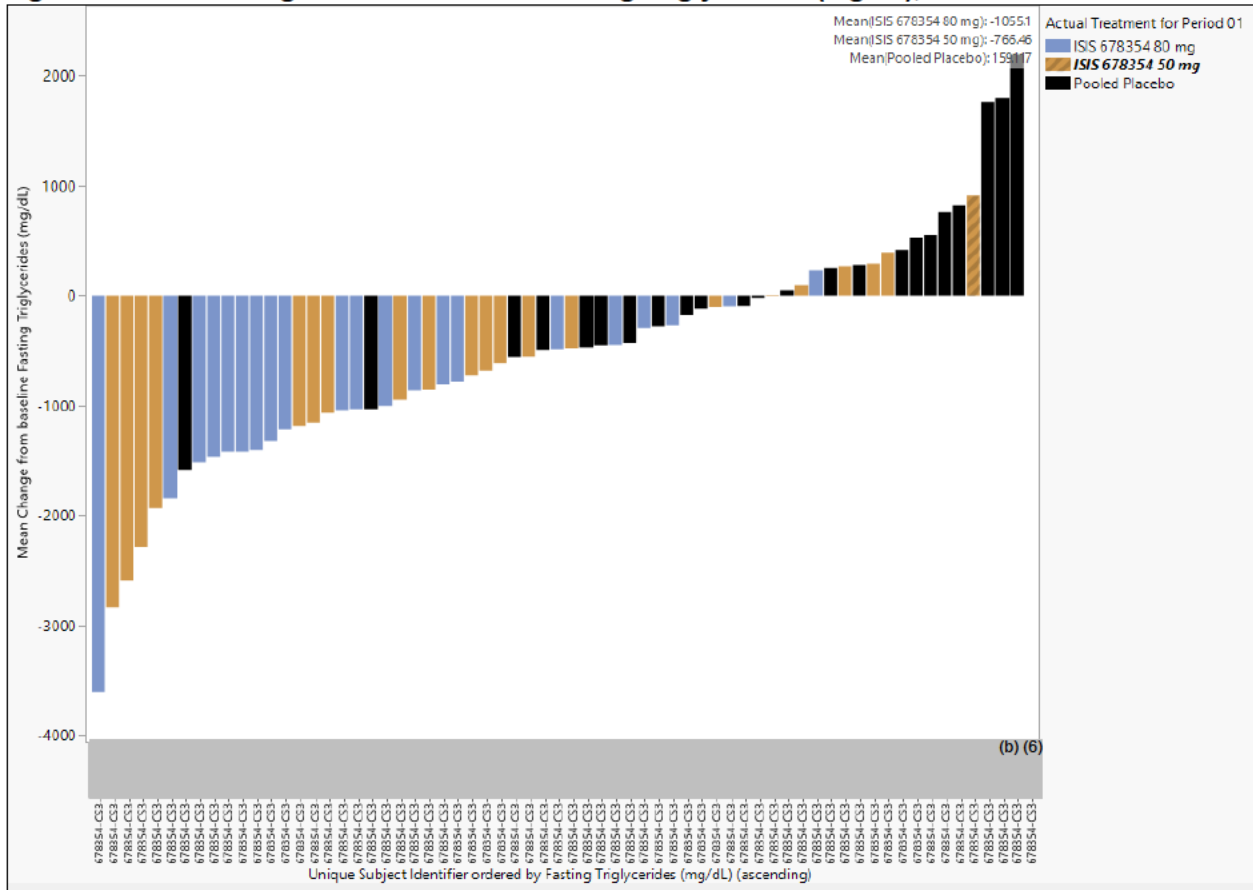
Figure 71. Mean (95% CI) Change From Baseline Fasting Triglycerides (mg/dL), Trial CS3



Source: Clinical Reviewer Analysis, JMP Clinical
 Abbreviations: CI, confidence interval

[Figure 72](#) shows a waterfall plot of the mean change from baseline in fasting TG levels for the treatment arms in Trial CS3 over the 53-week treatment period.

Figure 72. Mean Change From Baseline in Fasting Triglycerides (mg/dL), Trial CS3

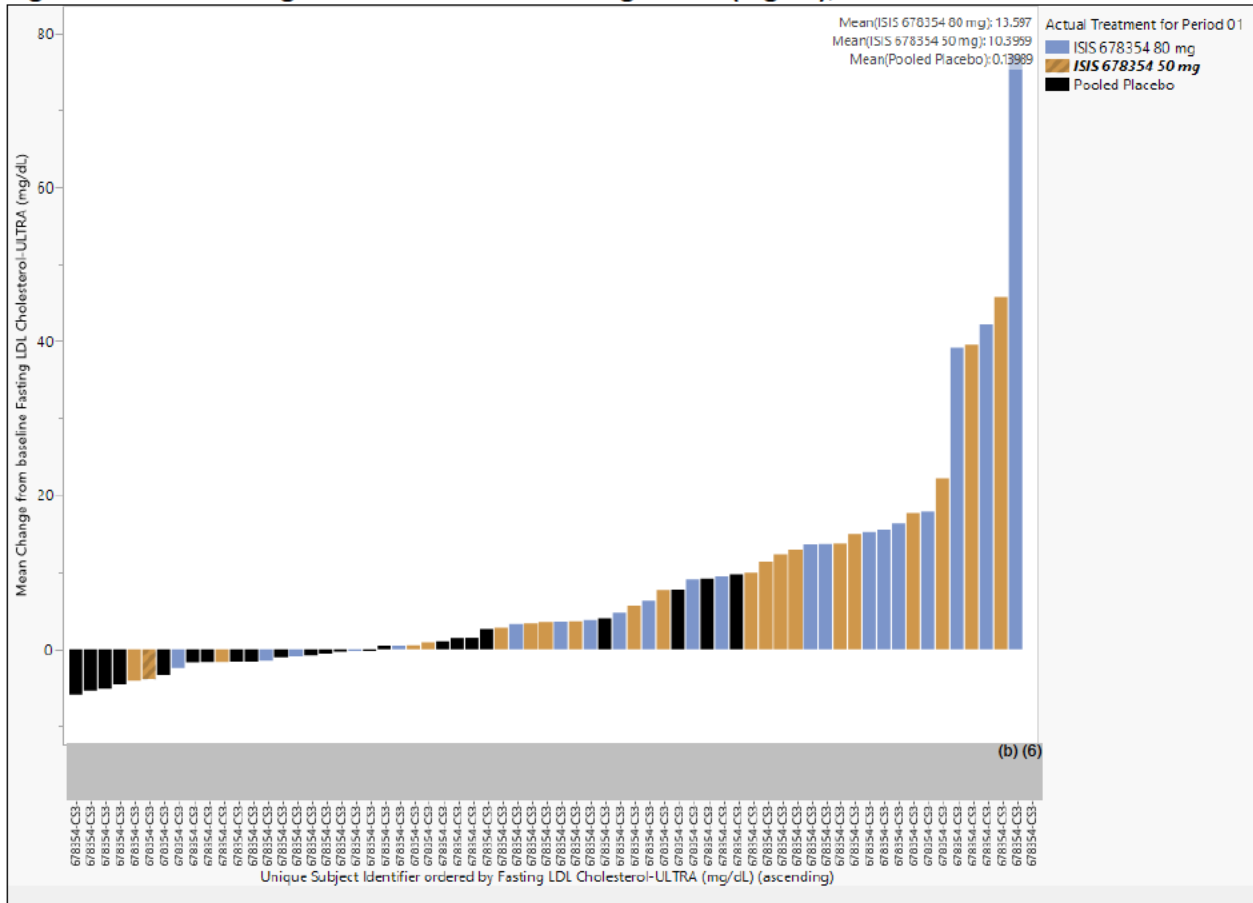


Source: Clinical Reviewer Analysis, JMP Clinical

The TG waterfall plot displays each individual subject's TG level change and is a visual representation of the effectiveness of olezarsen 80 mg treatment.

Figure 73 shows the mean change from baseline in LDL-C as a waterfall plot of all the subjects in Trial CS3.

Figure 73. Mean Change From Baseline in Fasting LDL-C (mg/dL), Trial CS3

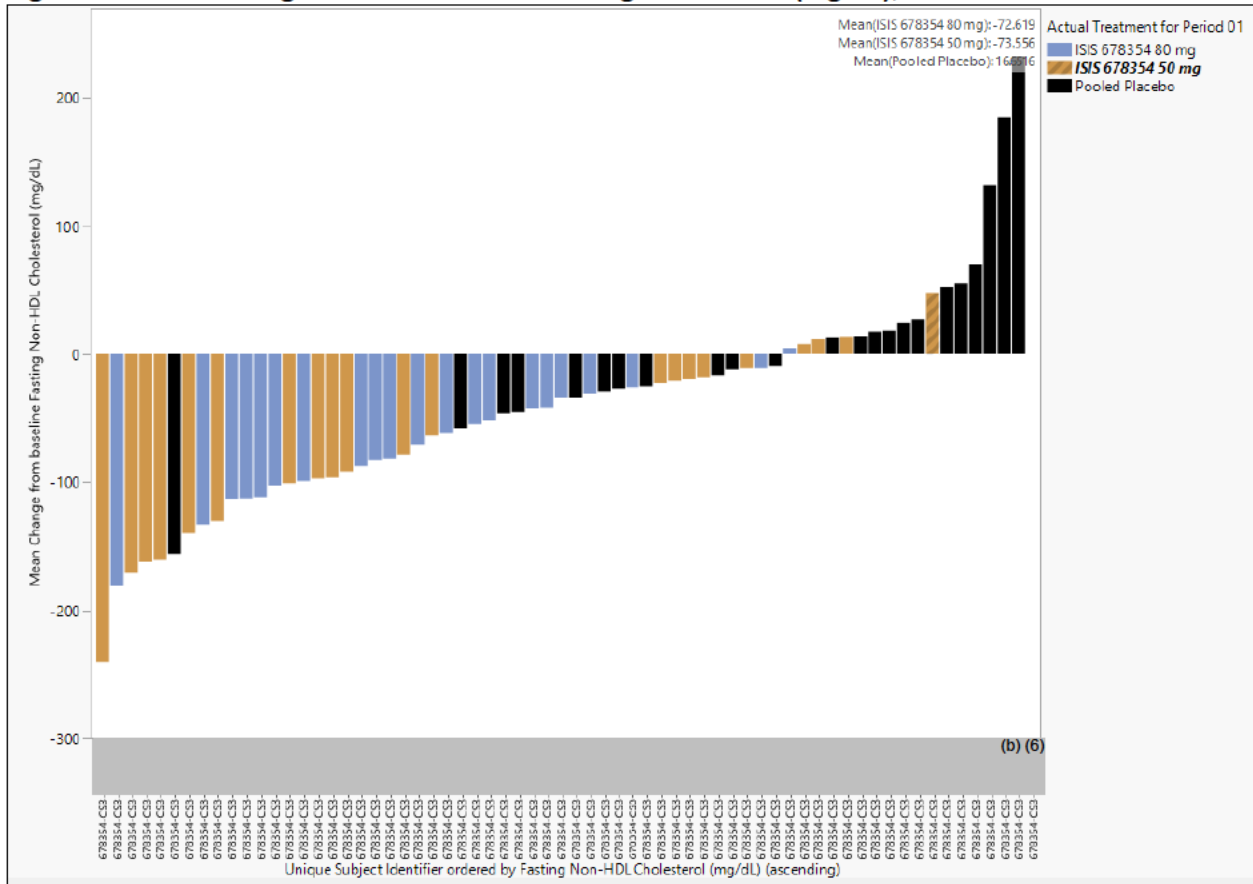


Source: Clinical Reviewer Analysis, JMP Clinical
 Abbreviations: LDL-C, low-density lipoprotein cholesterol

As shown in [Figure 73](#) above, LDL-C increased in subjects on olezarsen treatment as compared to subjects on placebo. An increase in LDL-C following TG-lowering therapy often occurs because treatments that reduce TG tend to reduce VLDL particles, which are rich in TG. As VLDL is metabolized, some of it is converted into LDL particles, thus increasing the overall amount of LDL-C in circulation. Because subjects with FCS have very low levels of LDL-C, the increase in LDL-C more often remains within the normal range for LDL-C levels. However, clinicians will need to evaluate and monitor subjects' LDL-C levels, especially those at higher cardiovascular risk.

[Figure 74](#) shows the mean change in non-HDL-C as a waterfall plot for all subjects in Trial CS3 over the 53-week treatment period.

Figure 74. Mean Change From Baseline in Fasting Non-HDL-C (mg/dL), Trial CS3

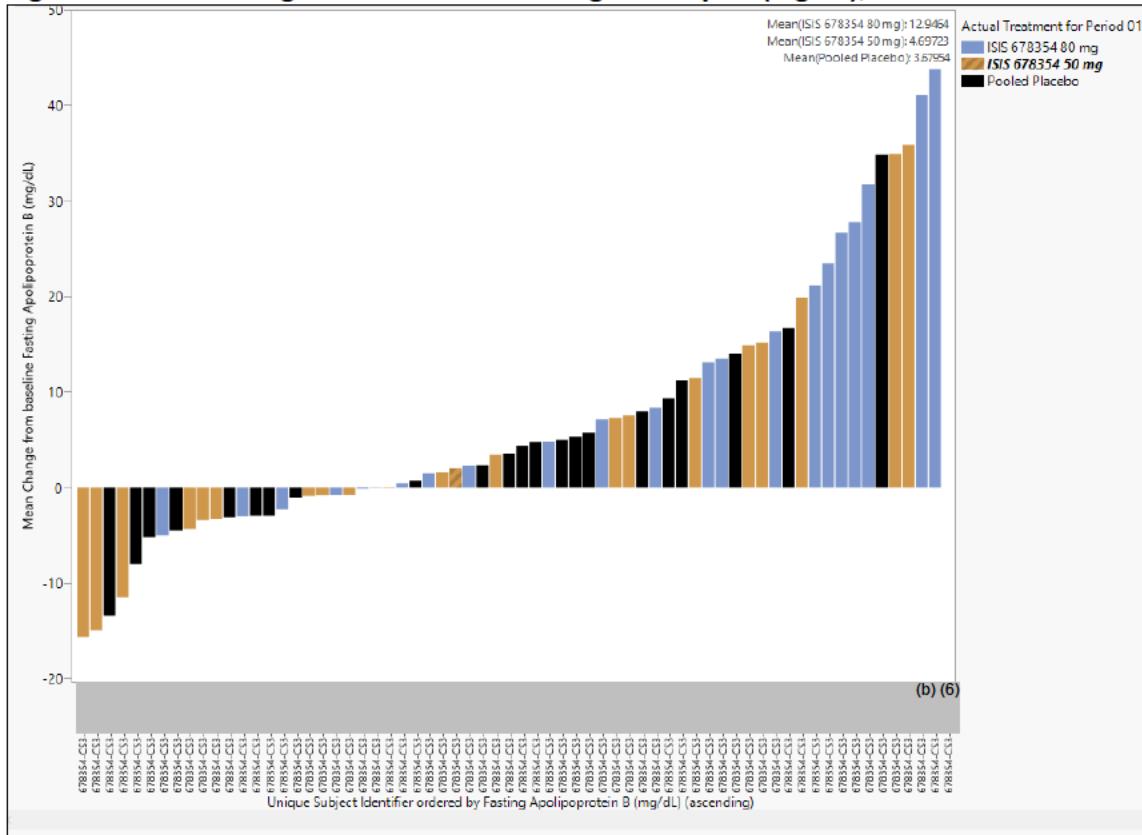


Source: Clinical Reviewer Analysis, JMP Clinical
 Abbreviations: HDL-C, high-density lipoprotein cholesterol

Non-HDL-C is a measure of all the cholesterol carried by lipoproteins other than HDL. Non-HDL-C includes LDL-C, VLDL-C, and intermediate-density lipoprotein cholesterol. As shown in Figure 74 above, non-HDL-C levels decreased with olezarsen 80 mg to a greater degree than placebo. Although non-HDL-C does not measure TG directly, high levels of TG often correlate with elevated VLDL cholesterol, and lower levels of TG correlate with lower levels of VLDL-C, which is part of the non-HDL-C value.

The following waterfall plot depicts mean CFB in total ApoB.

Figure 75. Mean Change From Baseline Fasting Total ApoB (mg/dL), Trial CS3

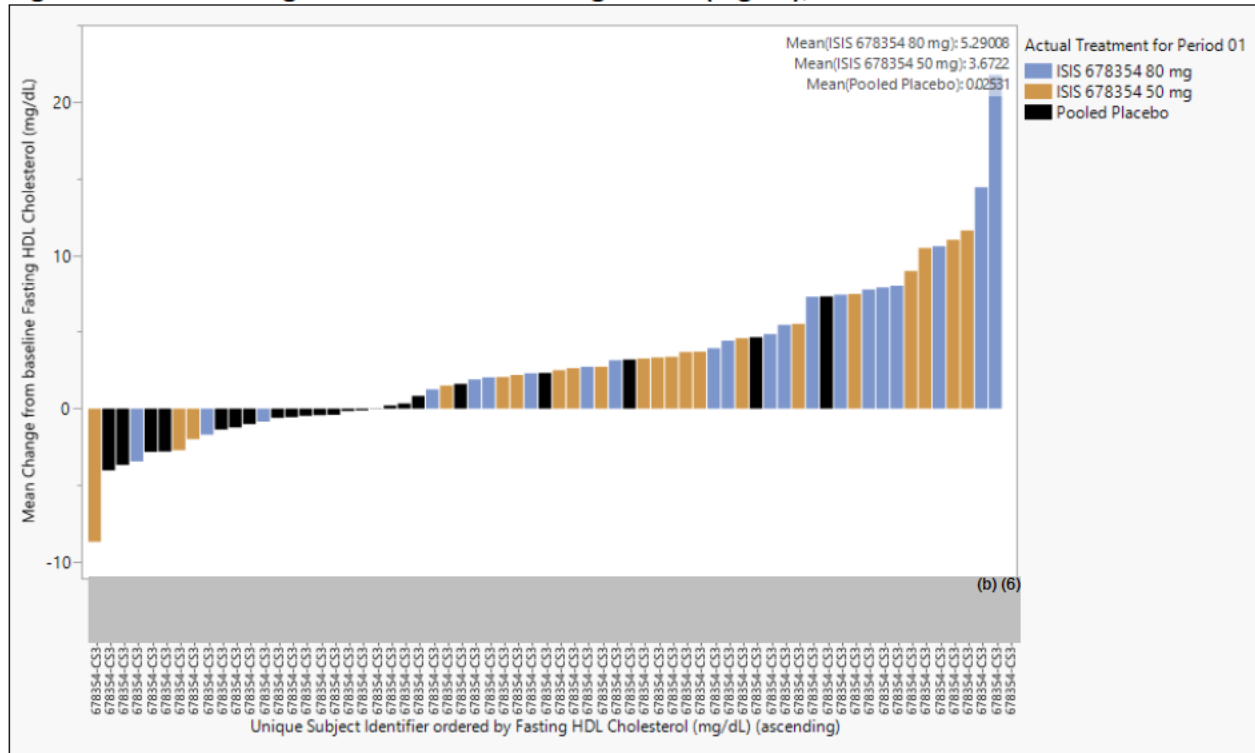


Source: Clinical Reviewer Analysis, JMP Clinical
 Abbreviations: ApoB, apolipoprotein B

Total ApoB is a measure of the total number of atherogenic lipoproteins in the blood. ApoB is a protein found on the surface of certain lipoproteins, including LDL-C, VLDL-C, intermediate-density lipoprotein and lipoprotein(a). The increase in total ApoB may reflect the increase in LDL-C seen with olezarsen treatment.

Figure 76 depicts a waterfall plot of the mean change from baseline in HDL-C for Trial CS3.

Figure 76. Mean Change From Baseline Fasting HDL-C (mg/dL), Trial CS3



Source: Clinical Reviewer Analysis, JMP Clinical
 Abbreviations: HDL-C, high-density lipoprotein cholesterol

HDL-C helps transport cholesterol levels from the bloodstream and tissues back to the liver, where it can be processed and removed from the body. In observational studies, higher levels of HDL-C are associated with a lower risk of heart disease. However, human genetics and failed clinical trials have created uncertainties about targeting HDL-C to reduce CV risk (Rader and Hovingh 2014). As shown in Figure 76 above, treatment with olezarsen (both doses) increased levels of HDL-C as compared to placebo. However, the clinical implications of the increases in HDL-C in the FCS population are unknown.

16.3. Trial ISIS 678354-CS3, Clinical Outcome Assessment

This section briefly reviews the PROs and COAs for the evaluation of clinical benefit. Refer to the full Division of Clinical Outcome Assessment review for a detailed review.

Familial Chylomicronemia Syndrome Symptoms and Impacts Scale

The FCS-SIS is a 17-item PRO instrument designed to assess FCS symptoms and associated impacts. It consists of two domains: symptom domain (4 items) and impact domain (13 items). Items in the symptom domain are rated on an 11-point numeric rating scale ranging from 0 (“No [symptom]”) to 10 (“worst possible [symptom]”). Items in the impact domain are rated on a verbal rating scale ranging from “Never” to “Always.” The recall period for the symptom

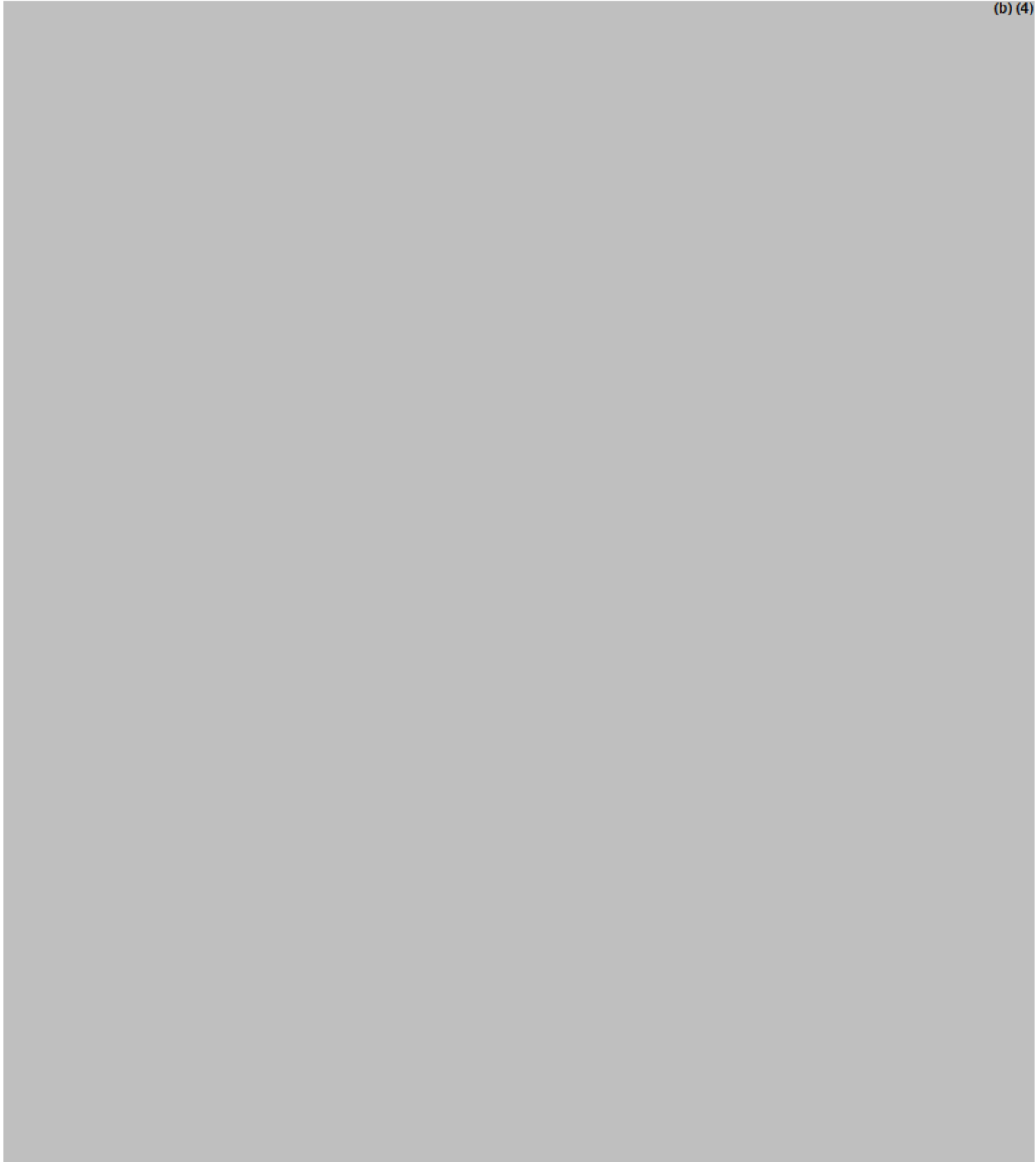
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domain is the previous two weeks.⁹ The recall period for the impact domain is momentary (“currently”). The FCS symptom domain (2-week recall) was administered at baseline, thereafter the 24-hour recall version was administered daily (minimum of 4 daily assessments per week) at baseline to Week 17. The FCS impacts scale was administered at screening, baseline, and then Q4W thereafter. See [Figure 77](#) for a copy of the instrument (24-hour recall version and impacts scales).

⁹ There are two versions of the Symptoms Domain, one with a recall period of “past 24 hours” (referred to as FCS Symptom) and another with a 2-Week recall period (referred to as FCS Symptoms Two Week Recall). Note the two week recall version was administered at screening and the 24-hour recall version was administered at baseline and postbaseline visits.

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Figure 77. FCS-SIS (24-Hour Recall Version and Impacts Scales)



(Figure 77 continued)



Source: ISIS 678354-CS3 Amendment 9 dated August 2, 2023, Appendix E.
Abbreviations: FCS, familial chylomicronemia syndrome; FCS-SIS, Familial Chylomicronemia Syndrome Symptoms and Impacts Scale

Review of COAs for Evaluation of Clinical Benefit

The Applicant did not submit an evidence dossier for any of the COAs and/or evidence to assess the fitness-for-purpose of the measures utilized in Trial CS3. Therefore, these instruments could not be reviewed for content validity, other measurement properties, and clinically meaningful change. In the absence of evidence, the FDA cannot make a definitive conclusion as to whether the COAs can support regulatory decision-making.

The Applicant conducted an exit interview substudy to provide further support for the content validity of the FCS-SIS and to facilitate the interpretation of the olezarsen clinical trial results. While the Applicant generated qualitative data to interpret olezarsen clinical trial results, the data are difficult to interpret due to limitations of the substudy (i.e., exit interviews conducted in the OLE phase of Trial CS3).

The data from Trial CS3 demonstrated that for olezarsen (80 mg and 50 mg) there was no change from baseline differences in any of the PRO scores compared with placebo. However, the data

from the exit interview substudy indicated that a total of 14 of the 18 patients (78%) reported improvement in at least one of their pre-trial symptoms and impacts and most improvements were considered meaningful.

In the absence of evidence, the Applicant has not demonstrated that any of the COAs are fit-for-purpose in the specified context of use. Further, the findings from Trial CS3 and exit interview substudy were not conclusive with improvements in FCS symptoms and impacts (median change was generally 0 in the FCS-SIS measure). As such, it is difficult to determine whether any treatment benefits were observed as they relate to FCS symptoms and impacts.

Refer to the full Division of Clinical Outcome Assessment review for a detailed review of the COAs and exit interview substudy.

17. Clinical Safety

Chemistry Laboratory Tables–Trial CS8

The following tables provide information regarding chemistry laboratories by certain thresholds for Trial CS8. No clinically significant differences were observed with the exception of glucose values.

Table 127. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial CS8

Laboratory Parameter	Olezarsen	Olezarsen	Placebo N=39 n/N _w (%)	Olezarsen	Olezarsen
	50 mg N=58 n/N _w (%)	80 mg N=57 n/N _w (%)		50 mg vs. Placebo Risk Difference % (95% CI)	80 mg vs. Placebo Risk Difference % (95% CI)
Sodium, low (mEq/L)					
Level 1 (<132)	1/58 (1.7)	1/57 (1.8)	1/39 (2.6)	-0.8 (-11.7, 7.0)	-0.8 (-11.7, 7.1)
Level 2 (<130)	0/58 (0)	1/57 (1.8)	1/39 (2.6)	-2.6 (-13.3, 3.8)	-0.8 (-11.7, 7.1)
Level 3 (<125)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Sodium, high (mEq/L)					
Level 1 (>150)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 2 (>155)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (>160)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Potassium, low (mEq/L)					
Level 1 (<3.6)	6/58 (10.3)	7/57 (12.3)	3/39 (7.7)	2.7 (-11.3, 14.6)	4.6 (-9.6, 17.1)
Level 2 (<3.4)	1/58 (1.7)	1/57 (1.8)	1/39 (2.6)	-0.8 (-11.7, 7.0)	-0.8 (-11.7, 7.1)
Level 3 (<3)	0/58 (0)	1/57 (1.8)	0/39 (0)	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Potassium, high (mEq/L)					
Level 1 (>5.5)	1/58 (1.7)	4/57 (7.0)	3/39 (7.7)	-6.0 (-18.9, 2.7)	-0.7 (-14.2, 10.5)
Level 2 (>6)	0/58 (0)	2/57 (3.5)	0/39 (0)	0.0 (-9.1, 6.3)	3.5 (-5.7, 12.0)
Level 3 (>6.5)	0/58 (0)	1/57 (1.8)	0/39 (0)	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Chloride, low (mEq/L)					
Level 1 (<95)	3/58 (5.2)	4/57 (7.0)	1/39 (2.6)	2.6 (-8.6, 12.1)	4.5 (-6.9, 14.7)
Level 2 (<88)	0/58 (0)	1/57 (1.8)	0/39 (0)	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Level 3 (<80)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Chloride, high (mEq/L)					
Level 1 (>108)	2/58 (3.4)	6/57 (10.5)	5/39 (12.8)	-9.4 (-23.8, 1.3)	-2.3 (-17.6, 10.8)
Level 2 (>112)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (>115)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

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Laboratory Parameter	Olezarsen 50 mg N=58 n/N_w (%)	Olezarsen 80 mg N=57 n/N_w (%)	Placebo N=39 n/N_w (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Bicarbonate, low (mEq/L)					
Level 1 (<20)	1/58 (1.7)	3/57 (5.3)	0/39 (0)	1.7 (-7.4, 9.2)	5.3 (-4.0, 14.4)
Level 2 (<18)	0/58 (0)	1/57 (1.8)	0/39 (0)	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Level 3 (<15)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Bicarbonate, high (mEq/L)					
Level 3 (>30)	29/58 (50.0)	17/57 (29.8)	14/39 (35.9)	14.1 (-6.2, 32.9)	-6.1 (-25.3, 12.7)
Glucose, low (mg/dL)					
Level 1 (<70)	3/58 (5.2)	1/57 (1.8)	1/39 (2.6)	2.6 (-8.6, 12.1)	-0.8 (-11.7, 7.1)
Level 2 (<54)	1/58 (1.7)	0/57 (0)	0/39 (0)	1.7 (-7.4, 9.2)	0.0 (-9.1, 6.4)
Level 3 (<40)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Glucose, fasting, high (mg/dL)					
Level 1 (≥100 to 125)	17/58 (29.3)	17/57 (29.8)	6/39 (15.4)	13.9 (-3.7, 29.7)	14.4 (-3.3, 30.3)
Level 2 (≥126)	41/58 (70.7)	40/57 (70.2)	33/39 (84.6)	-13.9 (-29.7, 3.7)	-14.4 (-30.3, 3.3)
Glucose, random, high (mg/dL)					
Level 2 (≥200)	1/12 (8.3)	2/4 (50.0)	1/3 (33.3)	-25.0 (-74.2, 15.5)	16.7 (-52.4, 71.5)
Level 3 (>250)	1/12 (8.3)	1/4 (25.0)	0/3 (0)	8.3 (-51.2, 36.5)	25.0 (-43.8, 72.3)
Calcium, low (mg/dL)					
Level 1 (<8.4)	2/58 (3.4)	3/57 (5.3)	1/39 (2.6)	0.9 (-10.1, 9.6)	2.7 (-8.5, 12.3)
Level 2 (<8)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (<7.5)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Calcium, high (mg/dL)					
Level 1 (>10.5)	5/58 (8.6)	6/57 (10.5)	6/39 (15.4)	-6.8 (-22.3, 6.2)	-4.9 (-20.6, 8.7)
Level 2 (>11)	1/58 (1.7)	1/57 (1.8)	0/39 (0)	1.7 (-7.4, 9.2)	1.8 (-7.4, 9.4)
Level 3 (>12)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Magnesium, low (mg/dL)					
Level 1 (<1.5)	5/58 (8.6)	3/57 (5.3)	4/39 (10.3)	-1.6 (-16.1, 10.4)	-5.0 (-19.1, 6.0)
Level 2 (<1.2)	2/58 (3.4)	1/57 (1.8)	1/39 (2.6)	0.9 (-10.1, 9.6)	-0.8 (-11.7, 7.1)
Level 3 (<0.9)	1/58 (1.7)	1/57 (1.8)	1/39 (2.6)	-0.8 (-11.7, 7.0)	-0.8 (-11.7, 7.1)
Magnesium, high (mg/dL)					
Level 1 (>2.3)	13/58 (22.4)	9/57 (15.8)	5/39 (12.8)	9.6 (-6.9, 24.4)	3.0 (-12.9, 17.1)
Level 2 (>4)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (>7)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Phosphate, low (mg/dL)					
Level 1 (<2.5)	7/58 (12.1)	5/57 (8.8)	2/39 (5.1)	6.9 (-6.2, 18.8)	3.6 (-9.2, 14.8)
Level 2 (<2)	0/58 (0)	1/57 (1.8)	0/39 (0)	0.0 (-9.1, 6.3)	1.8 (-7.4, 9.4)
Level 3 (<1.4)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Protein, total, low (g/dL)					
Level 1 (<6)	1/58 (1.7)	0/57 (0)	1/39 (2.6)	-0.8 (-11.7, 7.0)	-2.6 (-13.3, 3.9)
Level 2 (<5.4)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (<5)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Albumin, low (g/dL)					
Level 1 (<3.1)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 2 (<2.5)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (<2)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
CPK, high (U/L)					
Level 1 (>3X ULN)	3/58 (5.2)	8/57 (14.0)	2/39 (5.1)	0.0 (-12.4, 10.0)	8.9 (-4.5, 21.3)
Level 2 (>5X ULN)	1/58 (1.7)	4/57 (7.0)	0/39 (0)	1.7 (-7.4, 9.2)	7.0 (-2.3, 16.8)
Level 3 (>10X ULN)	1/58 (1.7)	1/57 (1.8)	0/39 (0)	1.7 (-7.4, 9.2)	1.8 (-7.4, 9.4)

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs. Placebo	80 mg vs. Placebo
	N=58	N=57	N=39	Risk Difference	Risk Difference
	n/N _w (%)	n/N _w (%)	n/N _w (%)	% (95% CI)	% (95% CI)
Blood urea nitrogen, high (mg/dL)					
Level 1 (>23)	19/58 (32.8)	20/57 (35.1)	18/39 (46.2)	-13.4 (-32.6, 6.3)	-11.1 (-30.5, 8.8)
Level 2 (>27)	9/58 (15.5)	13/57 (22.8)	7/39 (17.9)	-2.4 (-19.1, 12.4)	4.9 (-12.6, 20.7)
Level 3 (>31)	6/58 (10.3)	7/57 (12.3)	2/39 (5.1)	5.2 (-7.8, 16.7)	7.2 (-6.1, 19.2)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Renal-Related Labs–Trial CS8

No clinically significant differences were observed in Trial CS8.

Table 128. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial CS8

Laboratory Parameter	Olezarsen	Olezarsen	Placebo	Olezarsen	Olezarsen
	50 mg	80 mg		50 mg vs. Placebo	80 mg vs. Placebo
	N=58	N=57	N=39	Risk Difference	Risk Difference
	n/N _w (%)	n/N _w (%)	n/N _w (%)	% (95% CI)	% (95% CI)
Creatinine, high (mg/dL)					
Level 1 (≥1.5X baseline)	2/58 (3.4)	4/57 (7.0)	2/39 (5.1)	-1.7 (-13.9, 7.5)	1.9 (-10.7, 12.6)
Level 2 (≥2X baseline)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (≥3X baseline)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
eGFR, low (mL/min/1.73 m ²)					
Level 1 (≥25% decrease)	11/58 (19.0)	10/57 (17.5)	11/39 (28.2)	-9.2 (-27.2, 7.6)	-10.7 (-28.5, 6.1)
Level 2 (≥50% decrease)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)
Level 3 (≥75% decrease)	0/58 (0)	0/57 (0)	0/39 (0)	0.0 (-9.1, 6.3)	0.0 (-9.1, 6.4)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 374 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Supplementary Information Regarding Key Safety Issue–Hypersensitivity

[Table 129](#) below summarizes the discontinuations related to hypersensitivity and/or flu-like reaction (FLR) in Trials CS3, CS8, CS13, CS7.

Table 129. Discontinuations of Study Drug Due to Hypersensitivity-Related Adverse Events, Trials CS3, CS8, CS13, and CS7

Subject Data	CS7 (b) (6)	CS13 (b) (6) VLN (b) (6)	CS13 (b) (6)	CS3 (b) (6) VLN (b) (6)	CS3 (b) (6) VLN (b) (6)	CS8 (b) (6)	CS8 (b) (6)
AE	Hyper-sensitivity	Hyper-sensitivity	Anaphylactic reaction	Chills, myalgia, arthralgia (FLR)	Flushing, chest discomfort, diarrhea, vomiting	Flushing	Injection site urticaria
Serious	Yes	Yes	Yes	No	No	No	No
Previous VLN treatment	Yes	Yes	Yes	Yes	Yes	No	No
Duration of VLN treatment	5 years	4 months	8 months	2 years	2 years	NA	NA
#doses of VLN	Not provided	12	Not provided	60	84	NA	NA
#doses of OLZ	2	2	20	4 (3 at 80; 1 at 50) reduced due to symptoms arthralgia after 2 nd dose	1	4	6
TTO	Day 27	Day 29	Day 563	Day 58 (arthralgia) Day 114 (chills, myalgia)	Day 1	Day 1	143 Days
Symptoms time after dose	Within 10 hours	2 minutes post 2 nd dose	5 minutes post 20 th injection	6 hours post 4 th injection	15 minutes post first dose	Same day experienced flushing with all injections	Same day
ADA	Negative	Positive	Positive	Positive	Positive	Positive	Positive
Titer	NA	Day 1 800 Day 29 3200, Day 57 6400	Day 1 of CS3 (OLZ): 400; Day 57: 800; Day 169: 800; Day 253: 1600; Day 365: 6400 CS13 BL: 25,600; Day 563: 6400, Day 575: 12,800; Day 640: 200	Turned positive during VLN Study CS6 Study Day 176 titer 200; Day 260 400; Day 358 1600; Study CS7 titers 50 to 100 Day 1 of CS3: 1600; Day 29 200; Day 57 1600; Day 85 6400; ET 6400	50 Note subject did not develop ADA during treatment with volanesorsen	Day 1 6400 Day 29 800 Day 85 3200	Day 169 200 Day 253 400 Day 365 400

NDA 218614
 Tryngolza (olezarsen sodium)

	CS7 (b) (6)	CS13 (b) (6) VLN (b) (6)	CS13 (b) (6)	CS3 (b) (6) VLN (b) (6)	CS3 (b) (6) VLN (b) (6)	CS8 (b) (6)	CS8 (b) (6)
Subject Data							
Treatment needed	Yes, loratadine, fexofenadine, managed at home	Yes (IM steroids, IVF, and antihistamine) Managed in clinic	Yes (steroids, antihistamine); Managed in ED	No	Yes (steroids, antihistamine)	No	Yes (antihistamine, hydrocortisone)
Recovered	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Source: CSR Narratives, Response to FDA information request SDN 14, Submitted July 24, 2024

Abbreviations: ADA, antidrug antibodies; AE, adverse event; CSR, clinical study report; ED, emergency department; ET, early termination; FLR, flu-like reaction; IM, intramuscular; IVF, intravenous fluids; OLZ, olezarsen; TTO, time to onset; VLN, volanesorsen

Supplementary Safety Review–Changes in Other Hematopoietic Parameters

Issue

Higher proportions of olezarsen 80 mg treated subjects compared to placebo-treated subjects reported an event in CS3 using the FMQ (narrow) search terms ‘anemia’ and ‘leukopenia’ and ‘anemia’ (both 50 mg and 80 mg olezarsen compared to placebo) in CS8.

Background

Because of the reduction in platelet count observed with olezarsen treatment, there was concern that other hematopoietic parameters may be adversely affected.

Assessment

Higher proportions of olezarsen 80 mg treated subjects compared to placebo-treated subjects reported an event in CS3 using the FMQ (narrow) search terms ‘anemia’ and ‘leukopenia’ and ‘anemia’ (both 50 mg and 80 mg olezarsen compared to placebo) in CS8.

Table 130. Patients With Adverse Events by Selected FDA Medical Query (Narrow), Safety Population, Trial CS3

System Organ Class FMQ (Narrow)	Olezarsen 50 mg N=21 n (%)	Olezarsen 80 mg N=22 n (%)	Placebo N=23 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)					
Anemia	1 (4.8)	3 (13.6)	2 (8.7)	-3.9 (-23.2, 15.6)	4.9 (-15.8, 26.5)
Leukopenia	0	1 (4.5)	0	0.0 (-14.6, 15.8)	4.5 (-10.4, 22.1)

Source: Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as any AE events starting or getting worse on or after the first dose of the study drug.

Duration is up to 400 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Abbreviations: CI, confidence interval; FMQ, FDA medical query; SOC, system organ class

Table 131. Patients With Adverse Events by Selected FDA Medical Query (Narrow), Safety Population, Trial CS8

System Organ Class FMQ (Narrow)	Olezarsen 50 mg N=58 n (%)	Olezarsen 80 mg N=57 n (%)	Placebo N=39 n (%)	Olezarsen 50 mg vs. Placebo Risk Difference % (95% CI)	Olezarsen 80 mg vs. Placebo Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)					
Anemia	2 (3.4)	3 (5.3)	1 (2.6)	0.9 (-10.1, 9.6)	2.7 (-8.5, 12.3)

Source: Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE starting or getting worse on or after the first dose of the study drug. Duration is up to 374 days.

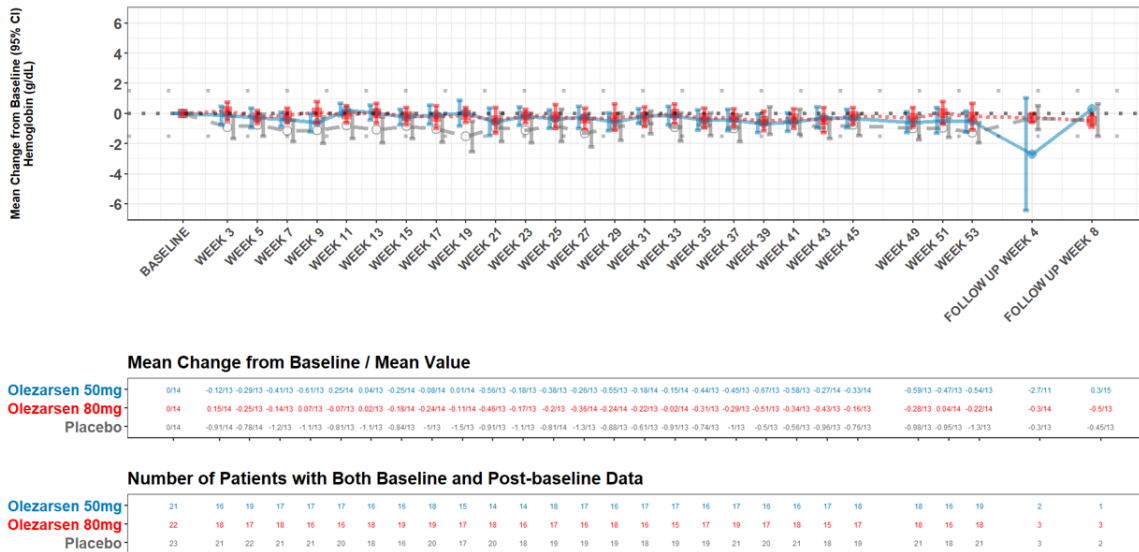
Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Abbreviations: CI, confidence interval; FMQ, FDA medical query; SOC, system organ class

No significant differences were noted in mean change from baseline in hemoglobin and white blood cell (WBC) over time in Trials CS3 and CS8 (see [Table 78](#), [Table 79](#), [Table 80](#), and [Table 81](#)).

Figure 78. Mean Change From Baseline Over Time – Hemoglobin, Trial CS3



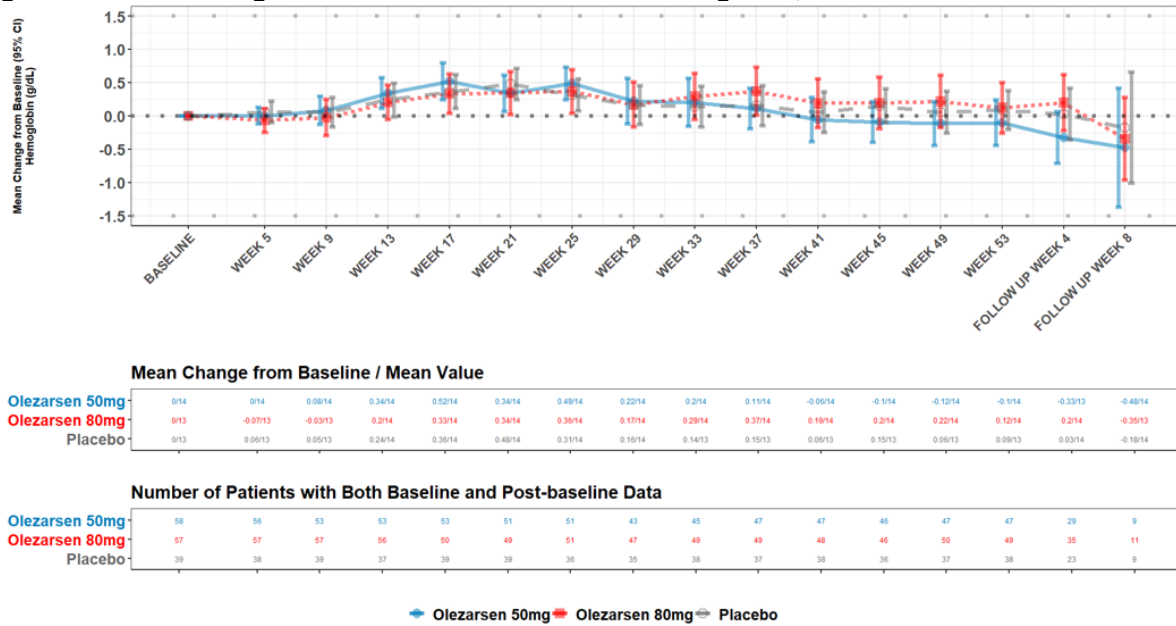
Source: Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.

Only central laboratory data are included in the analysis

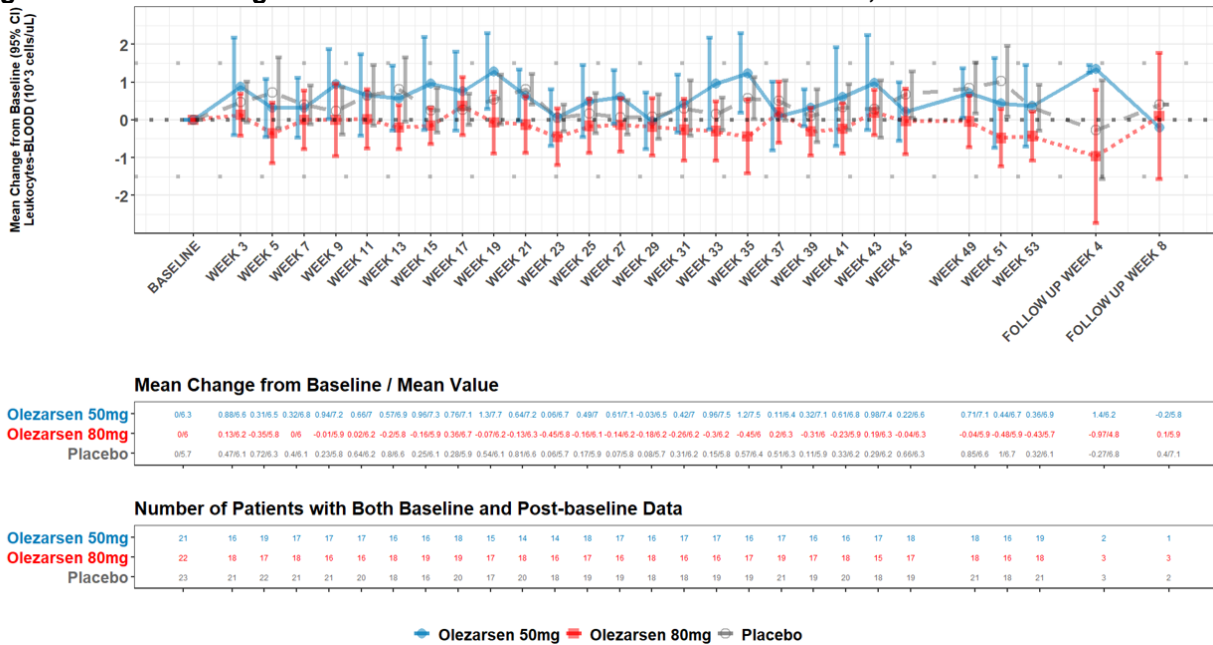
Abbreviations: CI, confidence interval

Figure 79. Mean Change From Baseline Over Time – Hemoglobin, Trial CS8



Source: Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Only central laboratory data are included in the analysis.
 Abbreviations: CI, confidence interval

Figure 80. Mean Change From Baseline Over Time – White Blood Cells, Trial CS3



Source: Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.

Only central laboratory data are included in the analysis

Abbreviations: CI, confidence interval

Figure 81. Mean Change From Baseline Over Time – White Blood Cells, Trial CS8



Source: Source: adlb.xpt; Software: R
 Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
 Only central laboratory data are included in the analysis.
 Abbreviations: CI, confidence interval

Small imbalances were noted when evaluating categorical changes in WBC, lymphocytes, and neutrophils in Trial CS3 and CS8. A higher percentage of olezarsen-treated subjects compared to placebo-treated subjects had a postbaseline value below certain thresholds for WBC, lymphocytes, and neutrophils. No significant difference was observed for categorical decreases of hemoglobin by 1.5 or 2 g/dL between treatment groups.

Table 132. Categorical Changes in Selected Hematopoietic Parameters, Trials CS3 and CS8

Parameter	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
WBC, low (cells/μL)						
<3500	0	4 (18.2)	5 (21.7)	3 (5.2)	3 (5.3)	1 (2.6)
<3000	0	3 (13.6)	3 (13.0)	1 (1.7)	0	0
<1000	0	0	0	0	0	0
Lymphocytes, low (cells/μL)						
<1000	5 (23.8)	10 (45.5)	10 (43.5)	13 (22.4)	9 (15.8)	4 (10.3)
<750	2 (9.5)	4 (18.2)	4 (17.4)	4 (6.9)	4 (7.0)	0
<500	1 (4.8)	2 (9.1)	2 (8.7)	1 (1.7)	0	0
Neutrophils (cells/μL)						
<2000	5 (23.8)	5 (22.7)	7 (30.4)	6 (10.3)	6 (10.5)	2 (5.1)
<1000	0	2 (9.1)	0	1 (1.7)	2 (3.5)	0
<500	0	1 (4.5)	0	0	0	0

Parameter	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
Hemoglobin, decrease (g/dL)						
>1.5 g/dL decrease from BL	11 (52.4)	10 (45.5)	16 (69.6)	8 (13.8)	6 (10.5)	5 (12.8)
>2 g/dL decrease from BL	8 (38.1)	7 (31.8)	11 (47.8)	3 (5.2)	5 (8.8)	2 (5.1)

Source: CS8 CSR Table 62; Numbers confirmed by CDS

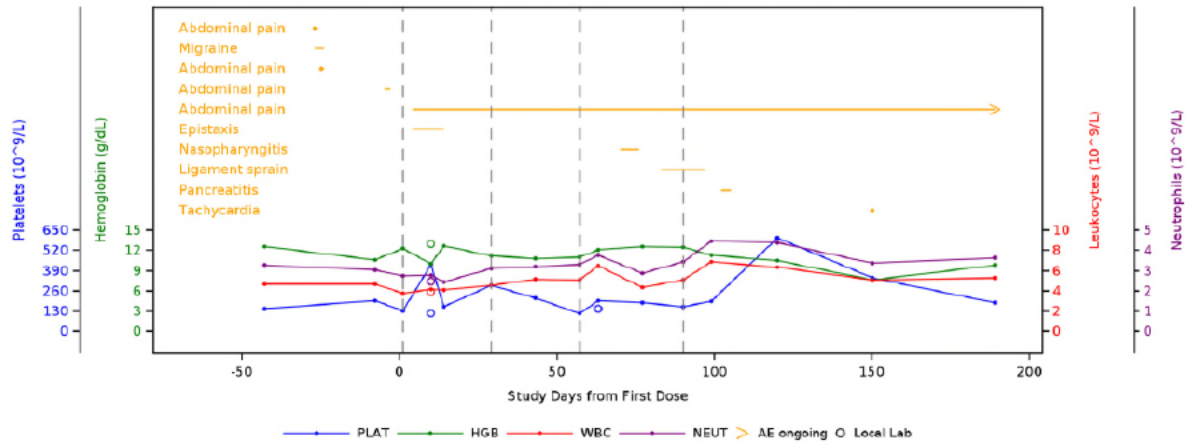
Abbreviations: BL, baseline; CDS, clinical data scientist; CSR, clinical study report; OLZ, olezarsen; PBO, placebo; WBC, white blood cells

In CS3, adverse shifts in Common Terminology Criteria for Adverse Event toxicity grades of ≥ 2 severity categories in hemoglobin occurred in three olezarsen-treated subjects and no placebo-treated subjects¹⁰. One of the three olezarsen-treated subjects (CS3-^{(b) (6)}) experienced a shift in hemoglobin from within reference range to a ‘severe’ category. This subject is described below:

- Subject CS3-^{(b) (6)} was treated with olezarsen 50 mg, experienced a reduction in hemoglobin from 12.3 g/dL (within reference range) at baseline to a nadir of 7.7 g/dL (severe) on Study Day 150. The subject had voluntarily withdrawn from the Trial CS3 on Study Day 114 (last dose of olezarsen Study Day 90) – she had recently been hospitalized for an episode of pancreatitis (Study Day 102). On the same day as the low hemoglobin (Study Day 150), the subject presented to the emergency department with chest pain. During the examination her heart rate was registered at 180 bpm. No abnormal troponin was reported. An ECG was performed which showed Atrioventricular Nodal Reentrant Tachycardia. She received 5 mg IV of adenosine. Her heart rate returned to sinus rhythm, and she was discharged. The subject’s hemoglobin improved at the next study visit (also last visit – follow-up week 13, Study Day 189) to 9.9 g/dL (moderate) and ECG was normal.

¹⁰ CTCAE toxicity grades version 5: Mild=hemoglobin <LLN to 10.0 g/dL; Moderate=hemoglobin <10.0 to 8.0 g/dL; Severe=hemoglobin <8.0 g/dL

Figure 82. Subject CS3- (b) (6) Graphical Subject Profile
 Subject Disposition: Withdrawal from Treatment (b) (6), Reason: Withdrawal by Subject, Complete follow-up (b) (6)



Central Lab Reference Range for Subject 678354-CS3- (b) (6) Hemoglobin: LLN=12, ULN=16; White Blood Cell: LLN=3.5, ULN=11; Neutrophils: LLN=1, ULN=8; Platelet Counts: LLN=140, ULN=400.
 Note 1: Study day is relative to the first dose date.
 Note 2: Both scheduled and unscheduled visit are included.
 Note 3: Vertical dashed lines represent actual dosing days.
 Note 4: Both Central Lab and local Lab are included.

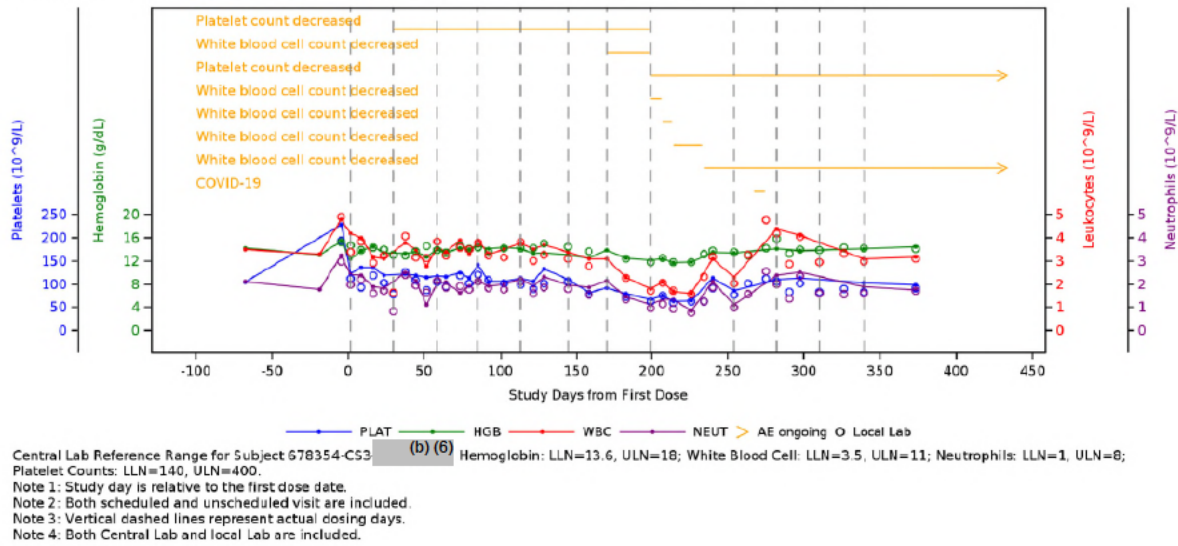
Source: Response to Division IR; SDN 22; August 16, 2024; Figure 1.1
 Abbreviations: AE, adverse event; HGB, hemoglobin; LLN, lower limit of normal; NEUT, neutrophils; PLAT, platelets; ULN, upper limit of normal; WBC, white blood cells

In CS3, one olezarsen-treated and one placebo-treated subject experienced an adverse shift in toxicity grades of ≥ 2 severity categories in WBC¹¹. The olezarsen-treated subject is described below:

- CS3- (b) (6) treated with olezarsen 80 mg group went from ‘within reference range’ to ‘severe’ with a baseline WBC of $4.2 \times 10^9/L$ that went to a nadir of $1.64 \times 10^9/L$ (local lab) ‘severe’ on Study Day 29, which improved to $3.8 \times 10^9/L$ (within reference range) at Study Day 37 without study drug changes or treatments. The subject again experienced a drop in WBC on Study Day 225 (week 33) of $1.6 \times 10^9/L$ ‘severe’ along with a drop in platelet count (platelet count $65 \times 10^9/L$). Study drug was interrupted. On Study Day 254 (Week 37) olezarsen treatment was resumed since platelet count and WBC had increased but remained low but similar to baseline values (note screening value was $3.5 \times 10^9/L$; reference range 3.5 to $11 \times 10^9/L$).

¹¹ CTCA toxicity grades version 5: Mild=WBC <LLN to $3.0 \times 10^9/L$; Moderate=WBC <3.0 to $2.0 \times 10^9/L$; Severe=WBC < $2.0 \times 10^9/L$

Figure 83. Subject CS3- (b) (6) **Graphical Subject Profile**
Subject Disposition: Completed Treatment (b) (6), Withdrawal from follow-up (b) (6), Reason: Open Label Extension



Source: Response to Division IR; SDN 22; August 16, 2024; Figure 2.1
Abbreviations: AE, adverse event; HGB, hemoglobin; LLN, lower limit of normal; NEUT, neutrophils; PLAT, platelets; ULN, upper limit of normal; WBC, white blood cells

Significant reductions in white blood cells, lymphocytes, and neutrophils may lead to increased susceptibility to infections and infestations. There were no significant differences across treatment groups in the SOC of ‘Infections and infestations’ in Trials CS3 or CS8.

Conclusion

Small imbalances were noted with olezarsen treatment for AEs related to anemia and when evaluating categorical changes in WBC, lymphocytes, and neutrophils in Trials CS3 and CS8. No significant differences were noted in mean CFB in hemoglobin and WBC over time in Trials CS3 and CS8. No clinically meaningful consequences were observed in that there were no significant differences across treatment groups for evaluation of infections in CS3 or CS8.

Supplementary Safety Review–Renal Function

Background

Renal toxicity has been observed after administration of volanesorsen and other SC and IV administered antisense oligonucleotides ([Akcea Therapeutics 2024b](#)).

Assessment

Renal impairment was defined per Acute Renal Failure Standardised Medical Query (narrow and broad) and Acute Kidney Injury FMQ. In both CS3 and CS8, a higher proportion of placebo-treated subjects compared to olezarsen-treated subjects reported a renal-impairment related TEAE.

Table 133. Renal Impairment Treatment-Emergent Adverse Events, Trials CS3 and CS8

Adverse Event	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
Renal impairment TEAE ¹	0	0	2 (8.7)	2 (3.4)	1 (1.8)	5 (12.8)
Proteinuria	0	0	2 (8.7)	1 (1.7)	0	1 (2.6)
Blood creatine increased	0	0	0	0	1 (1.8)	0
Glomerular filtration rate decreased	0	0	0	1 (1.7)	0	3 (7.7)
Albuminuria	0	0	0	0	0	1 (2.6)

Source: CS3 CSR Table 51; CS8 CSR Table 49

¹ Defined as Acute Renal Failure SMQ (broad and narrow) and Acute Kidney Injury FMQ (broad)

Abbreviations: CSR, clinical study report; OLZ, olezarsen; PBO, placebo; TEAE, treatment-emergent adverse event

The number and percentage of subjects that had at least one postbaseline value exceeding specified level in the following renal function related parameters are shown in [Table 134](#) below. The placebo-treated groups in both CS3 and CS8 had a higher proportion of subjects with a renal function value meeting these criteria. There were no dose interruptions or permanent discontinuations due to renal function laboratory values in CS3 or CS13.

Table 134. Number (%) of Subjects With at Least One Postbaseline Value Exceeding Specified Levels of Renal-Related Parameters, Safety Population, Trials CS3 and CS8

Parameter	CS3			CS8		
	OLZ 50 mg N=21 n (%)	OLZ 80 mg N=22 n (%)	PBO N=23 n (%)	OLZ 50 mg N=58 n (%)	OLZ 80 mg N=57 n (%)	PBO N=39 n (%)
Serum creatinine ≥ 0.3 mg/dL than baseline	2 (4.5)	4 (18.2)	8 (34.8)	7 (12.1)	10 (17.5)	9 (23.1)
Serum creatinine $\geq 2x$ baseline	1 (4.8)	0	1 (4.8)	0	0	0
Serum creatinine $\geq 3x$ baseline	1 (4.8)	0	0	0	0	0
eGFR decrease $\geq 25\%$	9 (9.5)	2 (9.1)	5 (21.7)	11 (19.0)	10 (17.5)	11 (28.2)
eGFR decrease $\geq 30\%$	2 (9.5)	2 (9.1)	4 (17.4)	7 (12.1)	5 (8.8)	8 (20.5)
eGFR decrease $\geq 50\%$	0	0	1 (4.3)	0	0	0
eGFR decrease $\geq 75\%$	0	0	0	0	0	0
UACR ≥ 300 mg/g	0	3 (9.1)	1 (4.3)	6 (10.3)	3 (5.3)	5 (12.8)
UACR ≥ 500 mg/g	0	0	1 (4.3)	4 (6.9)	1 (1.8)	3 (7.7)
UACR ≥ 1200 mg/g	0	0	1 (4.3)	1 (1.7)	1 (1.8)	1 (2.6)
UPCR ≥ 500 mg/g	0	2 (9.1)	3 (13.0)	8 (13.8)	9 (15.8)	11 (28.2)
UPCR ≥ 1000 mg/g	0	0	2 (8.7)	4 (6.9)	4 (7.0)	4 (10.3)
UPCR ≥ 2000 mg/g	0	0	0	1 (1.7)	1 (1.8)	1 (2.6)

Source: CS3 CSR, Table 52; CS8 CSR Table 50

Abbreviations: CSR, clinical study report; OLZ, olezarsen; PBO, placebo; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

There were fewer subjects treated with olezarsen (9.5% olezarsen 50 mg, 22.7% olezarsen 80 mg) that met a protocol defined additional renal monitoring or stopping criteria compared to those treated with placebo (47.8%). The renal alert/stopping criteria were eGFR decrease of 25%, increase in serum creatinine >0.3 mg/dL from baseline, UACR >250 mg/g, or UPCR >500 mg/g.

NDA 218614

Tryngolza (olezarsen sodium)

Review of renal-related AEs and changes in renal laboratory values in the open-label trials and in the 90-day safety update did not impact the interpretation of the results from Trials CS3 and CS8.

Conclusion

There was no acute kidney injury signal in the trials supporting the FCS treatment indication.

Supplementary Information for Key Safety Review Issue–Immunogenicity

Subjects with a positive ADA status could be further classified into different ADA types based on their baseline ADA status and change in ADA titer post-treatment. These definitions are described in Section [17](#).

Treatment-Emergent ADA

Subjects with either treatment-induced ADA or treatment-boosted ADA as described below:

- Treatment-induced ADA: ADA developed de novo (seroconversion) following study drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA, i.e., baseline negative ADA).
- Treatment-boosted ADA: pre-existing ADA that were boosted to a higher level following study drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a factor of 8-fold or more).

Treatment-Unaffected

ADA: pre-existing ADA that were not affected (boosted) following study drug administration (i.e., any time after the initial drug administration the ADA titer is 4-fold or less).

Subjects with positive ADA status that was treatment-induced were also classified as being ‘transient’ or ‘persistent’ based on the following definitions.

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.

Table 135. Summary of Immunogenicity Status, Safety Set, Trial CS3

Immunogenicity Status	OLZ	OLZ	PBO	OLZ	OLZ	PBO
	50 mg	80 mg		50 mg	80 mg	
	N=21	N=22	N=23	N=58	N=57	N=39
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Positive postbaseline	12 (57.1)	13 (59.1)	9 (39.1)	28 (48.3)	29 (50.9)	11 (28.2)
Treatment-emergent	8 (38.1)	10 (45.5)	0	24 (41.4)	23 (40.4)	5 (12.8)
Treatment-induced	5 (23.8)	8 (36.4)	0	20 (34.5)	18 (31.6)	3 (7.7)
Transient	0	0	0	2 (3.4)	1 (1.8)	2 (5.1)
Persistent	5 (23.8)	8 (36.4)	0	18 (31.0)	17 (29.8)	1 (2.6)
Treatment-boosted	3 (14.3)	2 (9.1)	0	4 (6.9)	5 (8.8)	2 (5.1)
Treatment-unaffected	4 (19.0)	3 (13.6)	9 (39.1)	4 (6.9)	6 (10.5)	6 (15.4)
Negative	9 (42.9)	9 (40.9)	14 (60.9)	30 (51.7)	28 (49.1)	28 (71.8)
Baseline negative	8 (38.1)	8 (36.4)	13 (56.5)	28 (48.3)	27 (47.4)	27 (69.2)
Baseline positive	1 (4.8)	1 (4.5)	1 (4.3)	1 (1.7)	0	1 (2.6)
Baseline unknown	0	0	0	1 (1.7)	1 (1.8)	0
Subjects with positive ADA at baseline	8 (38.1)	6 (27.3)	10 (43.5)	9 (15.5)	11 (19.3)	9 (23.1)

Source: CSR CS3 Table 59; CSR CS8 Table 64; numbers confirmed by clinical reviewer using ADIP.xpt dataset

Positive: Patients have at least 1 confirmed positive sample result at any time during the treatment or post-treatment evaluation periods, which include the following:

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 patient without pre-existing ADA, i.e., Baseline negative ADA).

Treatment-Boosted ADA: pre-existing ADA that were boosted to a higher level following study drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the Baseline titer by a factor of 8-fold or more).

Treatment-Unaffected ADA: pre-existing ADA that were not affected (boosted) following study drug administration (i.e., any time after the initial drug administration the ADA titer is less than 8-fold).

Negative ADA: All evaluated immunogenicity sample results during the treatment and post-treatment evaluation periods are negative and have at least 1 evaluable immunogenicity result collected after the first dose of study drug. If a patient has only a positive sample at Baseline (Day 1 pre-dose) and negative at all other time points, the patient will have negative IM status.

Abbreviations: ADA, antidrug antibodies; CSR, clinical study report; OLZ, olezarsen; PBO, placebo

Pregnancy

There was one paternal exposure during pregnancy reported. Subject CS3-^{(b) (6)}, a 43-year-old man enrolled in Trial CS3 and randomized to olezarsen 80 mg (first dose on ^{(b) (6)}). On Study Day 8, the subject reported paternal exposure during pregnancy. The subject's partner was a 27-year-old, with first date of last menstrual period of ^{(b) (6)}, with expected delivery ^{(b) (6)}. The gestational age at the time of drug exposure was estimated to be week 5. Infant was born ^{(b) (6)}, via elective caesarian delivery. On ^{(b) (6)} (Study Day 219), the male infant experienced supra and infra tentorial morphological changes, and changes in the eyeballs/papilla and optic nerve that were suggestive of tubulinopathy. Per the infant's pediatrician, the diagnosis could be West Syndrome, but this was not confirmed.

On ^{(b) (6)} (Study Day 437), the infant, who was approximately 8 months old at this time, was hospitalized for muscle spasms. Treatment with anti-convulsive medication was initiated which stopped the involuntary movements. The infant was improving with physiotherapy to strengthen his muscles but was still unable to sit up.

Reviewer Comment

Discussion with the non-clinical review team regarding this case noted that in the fertility studies of both olezarsen and volanesorsen, drug treated males were mated with drug-treated females, so sex specificity of effects cannot be ascertained. However, there were no effects on fetal development reported with olezarsen. For volanesorsen, there were increases in rib variations (not statistically significant) noted in the offspring, but nothing analogous to the muscle spasms or eye issues reported clinically. In the pre-/postnatal toxicity study with volanesorsen in which pregnant females were treated throughout gestation and lactation, there were reductions in maternal body weights which resulted in lower pup weights at the HD of 25 mg/kg (approximately 25x the clinical dose based on BSA). The reduced pup weights in turn contributed to slight delays in the occurrence of various developmental landmarks. Delays of this nature are not unusual when there are effects on pup body weights.

Tissue distribution studies provide further support for the effect not being related to olezarsen. In the rat, testicular tissue levels averaged 0.2% of a single SC dose of 5 mg/kg (approximately 3-fold the clinical dose on a BSA basis). Given the low level in testicular tissue, targeted delivery to the liver if any drug in the ejaculate actually made it into the female circulatory system and across the placental barrier, it is improbable that treatment of the male partner led to the observed anomalies.

There are anecdotal case reports in the literature of women with FCS treated with volanesorsen during their pregnancies with successful outcomes for both mother and baby ([Wanninayake et al. 2024](#)).

Autoinjector

The to-be-marketed formulation of olezarsen will be an autoinjector. The autoinjector was introduced into the open-label clinical trials, CS7 and CS13. In CS13, at the time of the NDA submission there were 32 subjects administering olezarsen with the autoinjector with a mean exposure of 99 days (minimum 6 days, maximum 199 days). At the 90-day safety update, there were 56 subjects with a mean exposure of 151 days (minimum 28 days, maximum 317 days).

Use of the autoinjector in CS7 occurred after the data cutoff for both the NDA and 90-day safety update and therefore no information is available.

The amount of exposure to the autoinjector is small. Refer to the Human Factors and Center for Devices and Radiological Health reviews for acceptability of this device.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Two clinical site inspections and a Contract Research Organization (CRO) inspection were completed by the Office of Scientific Investigations. Based on the results of these inspections, Trials CS3 and CS8 appear to have been conducted adequately, and the clinical data generated by these sites appear to be reliable in support of this NDA.

The clinical sites were chosen using a risk-based approach primarily based on numbers of enrolled subjects, treatment effect, protocol deviations, and prior inspection history. The two sites included Seth Baum, M.D. (Site # 2138) and Alejandro De La Cruz, M.D. (Site # 3195).

1. Seth Baum, M.D. (Site # 2138)

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Boca Raton, FL 33434-4104
Inspection dates: August 5 to 7, 2024
Trials CS3 and CS8

This was the first FDA inspection of Dr. Baum. For Trial CS3, the site screened 9 subjects and enrolled 5 subjects. All 5 subjects completed the study. Source records for all 9 screened subjects were reviewed. For Trial CS8, the site screened 14 subjects and enrolled 7 subjects. Five subjects completed the study, and two subjects discontinued the study: 1 due to AE of GI disorder (olezarsen 50 mg group) and 1 due to GI cancer diagnosis (olezarsen 80 mg group). Source records for all 14 screened subjects were reviewed.

The inspection reviewed the trials' protocols and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records, investigational product (investigational product) accountability records, both paper and electronic Case Report Forms (eCRFs) and electronic data capture (EDC) system, protocol deviations and related regulatory documents. The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the mean percent change in fasting TG from baseline at Month 6 were centrally adjudicated and were initially blinded to the site. The inspection verified the results with no discrepancies noted. There were no underreporting of AEs or SAEs. In general, the

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inspection verified adequate source data for the inspected study subjects, with no deficiencies reported.

2. Alejandro De La Cruz, M.D. (Site # 3195)

13218 SW 8th Street Miami, FL 33184-1176

Inspection dates: July 8 to 16, 2024

Trial CS8

This was the first FDA inspection of Dr. De La Cruz. For Trial CS8, the site screened 64 subjects and enrolled 32 subjects. Except for one subject (olezarsen 50 mg group) who withdrew due to AE of ecchymosis at the injection site, 31 subjects completed the study. ICFs for 12/64 screened subjects, all source records for 11/32 of the enrolled subjects, and primary efficacy endpoint and AEs for all 32 randomized subjects were reviewed.

The inspection reviewed the protocol and amendments, English and Spanish language ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records, investigational product accountability records, paper CRFs with EDC entries and audit trails, protocol deviations and related regulatory documents. The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the mean percent change in fasting TG from baseline at Month 6 were verified with no discrepancies noted. There was no underreporting of SAEs. The inspection noted several protocol deviations to include three subjects that did not meet all inclusion or exclusion criteria and two AEs (“redness at the injection site” and “nausea”) that were recorded in source documentation but were not entered into the EDC. In general, the inspection verified adequate source data for the inspected subjects, with no significant deficiencies noted.

3. Medpace Inc. (CRO)

5400 Medpace Way

Cincinnati, OH 45227-1530

Inspection dates: July 8 to 11, 2024

Trials CS3 and CS8

This was the second FDA inspection of the CRO Medpace. Previous inspection was in February 2024 with no good clinical practice issues identified. For both trials, Medpace was responsible for clinical trial management, study startup and maintenance, subject recruitment and retention, clinical monitoring, Data and Safety Monitoring Board meeting organization and attendance; and biostatistics analysis for Trial CS8. The inspection reviewed the CRO’s standard operating procedures (SOPs), training records, monitoring records, site investigator documents, contracts with the Applicant and 3rd party vendors, meeting minutes, non-compliance issues management, Data and Safety Monitoring Board meeting documents, and biostatistics data transfer verification. Financial disclosure forms and monitoring files were reviewed for four sites for Trial CS3 and five sites for Trial CS8 with no good clinical practice issues identified.

In general, the CRO’s management and monitoring of Trials CS3 and CS8 appear adequate, with no significant deficiencies noted.

For additional details, refer to the review by Dr. Ling Yang, in Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated October 18, 2024; Reference ID: 5464827.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant’s draft PI submitted on April 19, 2024 ([Table 136](#)). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 136. Key Labeling Changes and Considerations

Full PI Sections¹	Rationale for Major Changes to Finalized PI² Compared to Applicant’s Draft PI
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	No major changes. Minor edits were made to the indication as it is not necessary to include the (b) (4) next to the tradename in the indication in the Full PI. This is only included in the Highlights section per 21 CFR 201.57(a)(5) and guidance for industry: <i>Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements</i> (February 2013b).
2 DOSAGE AND ADMINISTRATION	- Added information on how to handle a missed dose. - Added information that patients on olezarsen should maintain a low-fat diet (≤20g fat per day).
4 CONTRAINDICATIONS	Added details regarding the type of serious hypersensitivity reactions that have occurred.
5 WARNINGS AND PRECAUTIONS	Additional details regarding the type of serious hypersensitivity reactions that have occurred and mitigation strategies were added to the Warnings & Precautions of hypersensitivity.
6 ADVERSE REACTIONS	- Revised language for consistency with guidance for industry: <i>Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (January 2006). - Adverse reactions table was revised to reflect grouped terms composed of several similar terms. - Adverse reactions related to laboratory tests (decrease in platelet count, increase in glucose, increase in liver enzymes, increase in LDL-cholesterol and total apolipoprotein B) were added.
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	- Section 8.1 Pregnancy: Extensive edits were made to reflect the FDA’s interpretation of the animal data and to clarify the origin of these results. - Section 8.5 Geriatric Use: Revised language for consistency with the draft guidance for industry <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling</i> (September 2020).
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	Section 12.1 Mechanism of Action: Edits were made to reflect FDA’s conclusions and preferred wording (i.e., that is not potentially promotional).

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
13 NONCLINICAL TOXICOLOGY	Edits were made to reflect FDA's conclusions on the animal data and preferred wording. • The section was edited (b) (4) the data from the approved dosage of 80 mg (b) (4) • Throughout this section, (b) (4) • Table 2: (b) (4) the primary endpoint was at Month 6. (b) (4) Lipid parameters of LDL-C and total apoB were added to the table to describe the changes in lipid parameters related to ASCVD risk. Footnotes were added to describe the analysis method used and a clarification of the LDL-C results (i.e., mean LDL-C levels increased but (b) (4) remained within normal range). • (b) (4) • Incidence of acute pancreatitis: (b) (4) (b) (4) a short description of the findings that the numerical incidence of acute pancreatitis in patients treated with TRYNGOLZA 80 mg was lower compared with placebo (b) (4).
14 CLINICAL STUDIES	(b) (4) • Revised some of the language related to hypersensitivity.
17 PATIENT COUNSELING INFORMATION	• Revised some of the language related to hypersensitivity.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Minor edits were made to clarify the storage language once the autoinjector is removed from the refrigerator.

Source: FDA edits as of November 20, 2024, to the prescribing information from the Applicant dated November 13, 2024.

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviation(s): PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Carton labeling
- Container label
- Instructions for use
- Patient information
- Prescribing information

24. Postmarketing Requirements and Commitments

The following postmarketing requirement is recommended:

Complete the ongoing randomized, double-blind, placebo-controlled trials (ISIS 678354-CS5 [CORE] and ISIS 678354-CS6 [CORE 2]) and the two-year open-label extension (OLE) trial (ISIS 678354-CS15) to evaluate the potential for drug induced liver injury with Tryngolza.

Interim Report Submission (ISIS 678354-CS5, ISIS 678354-CS6 trial data; OLE 678354-CS15 trial): June 2026

Interim Report Submission (OLE 678354-CS15 trial): June 2027

Interim Report Submission (OLE 678354-CS15 trial): June 2028

Trial Completion: December 2028

Final Report Submission: June 2029

All three trials should be completed by the trial completion milestone and the final report submission should include data from all three trials.

25. Financial Disclosure

Table 137. Covered Clinical Studies: [Insert Study Names]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Trial CS3: 52; Trial CS8: 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

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Book

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27. Review Team

Table 138. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Ron Picking, PharmD
Chief, Project Management Staff	Elizabeth Solomon, MSHS, CCRP, RAC-drugs, GWCPM
Nonclinical reviewer	Njwen Anyangwe, PhD
Nonclinical team leader	Daniel Minck, PhD
OCP reviewer	Anusha Ande, PhD
OCP team leader	Li Li, PhD
Clinical reviewers	Mary Roberts, MD; Iffat Chowdhury, MD
Clinical team leader	Eileen Craig, MD
Biometrics reviewer	Kiya Hamilton, PhD
Biometrics team leader	Feng Li, PhD
COA Reviewer	Yasmin Choudhry, MD
COA Team Leader	Selena Daniels, PharmD, PhD
Pharmacometrics Reviewer	Elyes Dahmane, PhD
Pharmacometrics Team Leader	Justin Earp, PhD
OPQ	Akm Khairuzzaman, PhD
Cross-discipline team leader	Eileen Craig, MD
Associate Director for Labeling	Melinda Wilson, PharmD, MPH, BCPS, RAC
Division director (pharm/tox)	Lee Elmore, PhD
Division director (OCP)	Shirley Seo, PhD
Division director (OB)	Mark Rothmann, PhD
Division director (clinical)	John Sharretts, MD
Office director (or designated signatory authority)	Lisa Yanoff, MD

Abbreviations: COA, Clinical Outcomes Assessment; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OPQ, Office of Pharmaceutical Quality

Table 139. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQR	Ha Na Lee, PhD; Daniela Verthelyi, MD, PhD
CDRH	Farzaneh Akhavannik
OPDP	Ankur Kalola, PharmD
DMPP	Sharon Williams, MSN, BSN, RN; Marcia Williams, PhD
OSI	Ling Yang, MD, PhD; Min Lu, MD, MPH; Jenn Sellers, MD, PhD
OSE/DEPI	Po-Yin Chang, PhD; Yandong Qiang, MD, PhD, MHS, MPH
OSE/DMEPA	Vraj Patel, PharmD; Damon Birkemeier, PharmD, FISMP, NREMT
OSE/DMEPA Human Factors	Avinash Konkani, PhD, MS, BE; Matthew Barlow, RN, BSN
OSE/DRISK	Ingrid Chapman, PharmD, BCPS; Naomi Boston, PharmD
OSE/DPV	Ian Dunne, PharmD, BCPS; Daniel Woronow, MD, FACC; Ali Niak, MD
Cross-Discipline Safety Advisor	Christian Cao, MPAS, PA-C
IRT	Eliford Kitabi, PhD; Mario Sampson, PharmD; Christine Garnett, PharmD
DHN Consult	Eileen NavarroAlmario, MD; Paul Hayashi, MD; Edwige ChiogoVouffo, MD; Hobart Rogers, PharmD, PhD.
DARS Consult	Paula Hyland, Ph.D.; Wendy Wu, Ph.D.

Abbreviations: CDRH, Center for Devices and Radiological Health; DARS, Division of Applied Regulatory Science; DEPI, Division of Epidemiology; DHN, Division of Hepatology and Nutrition; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPV, Division of Pharmacovigilance; DRISK, Division of Risk Management; IRT, Interdisciplinary Review Team for Cardiac Safety Studies; OPDP, Office of Prescription Drug Promotion; OPQR, Office of Pharmaceutical Quality Research; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-140 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Justin Earp OCP DPM	Sections: 6.1, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Justin Earp		Digitally signed by Justin Earp		
		Date: 12/17/2024 5:05 PM EST GUID: 202412172259		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Elyes Dahmane OCP DPM	Sections: 6.1, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elyes Dahmane		Digitally signed by Elyes Dahmane		
		Date: 12/17/2024 5:08 PM EST		
		GUID: 202412172285		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Elyes Dahmane OCP DPM	Sections: 6.1, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elyes Dahmane		Digitally signed by Elyes Dahmane		
		Date: 12/17/2024 5:08 PM EST		
		GUID: 2024121722850		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Mary Roberts OCHEN DDLO	Sections: 7, 15, 17	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mary Roberts		Digitally signed by Mary Roberts Date: 12/17/2024 5:09 PM EST GUID: 2024121722940		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Secondary Reviewer	Selena Daniels ODES DCOA	Sections: 4, 16.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Selena Daniels		Digitally signed by Selena Daniels Date: 12/17/2024 5:15 PM EST GUID: 20241217221529		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Ronald Picking ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Ronald Picking		Digitally signed by Ronald Picking Date: 12/17/2024 5:15 PM EST GUID: 20241217221555		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline CPMS	Elizabeth Solomon ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Elizabeth Solomon		Digitally signed by Elizabeth Solomon Date: 12/17/2024 5:16 PM EST GUID: 20241217221640		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Li Li OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Li Li		Digitally signed by Li Li		
		Date: 12/17/2024 5:24 PM EST GUID: 20241217222428		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Yasmin Choudhry ODES DCOA	Sections: 4, 16.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yasmin Choudhry		Digitally signed by Yasmin Choudhry		
		Date: 12/17/2024 5:36 PM EST GUID: 20241217223623		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Yasmin Choudhry ODES DCOA	Sections: 4, 16.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yasmin Choudhry		Digitally signed by Yasmin Choudhry		
		Date: 12/17/2024 5:37 PM EST GUID: 2024121722374		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Melinda Wilson OCHEN DDLO	Sections: 23-26	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Melinda Wilson		Digitally signed by Melinda Wilson		
		Date: 12/17/2024 5:43 PM EST GUID: 20241217224324		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Melinda Wilson OCHEN DDLO	Sections: 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Melinda Wilson		Digitally signed by Melinda Wilson		
		Date: 12/17/2024 5:46 PM EST GUID: 20241217224646		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Feng Li OB DBII	Sections: 6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Feng Li		Digitally signed by Feng Li		
		Date: 12/17/2024 8:39 PM EST GUID: 2024121813915		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13.1-2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Calvin Elmore		Digitally signed by Calvin Elmore Date: 12/18/2024 8:11 AM EST GUID: 20241218131123		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Daniel Minck OCHEN DPTCHEN	Sections: 5, 7, 8.4, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Daniel Minck		Digitally signed by Daniel Minck Date: 12/18/2024 8:31 AM EST GUID: 20241218133151		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Mark Rothmann OB DBII	Sections: 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mark Rothmann		Digitally signed by Mark Rothmann		
		Date: 12/18/2024 8:43 AM EST GUID: 20241218134352		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Iffat Chowdhury OCHEN DDLO	Sections: 3,6,16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Iffat Chowdhury		Digitally signed by Iffat Chowdhury		
		Date: 12/18/2024 8:47 AM EST GUID: 20241218134758		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Anusha Ande OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Anusha Ande		Digitally signed by Anusha Ande Date: 12/18/2024 10:33 AM EST GUID: 20241218153339		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Daniel Minck OCHEN DPTCHEN	Sections: 5, 7, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Daniel Minck		Digitally signed by Daniel Minck Sign on behalf of Proxy for Njwen Date: 12/18/2024 11:05 AM EST GUID: 202412181651		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Product Quality Reviewer Discipline Primary Reviewer	Akm Khairuzzaman OPQAI DPQAI	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Akm Khairuzzaman		Digitally signed by Akm Khairuzzaman Date: 12/18/2024 11:40 AM EST GUID: 20241218164010		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Mohan Sapru OPQAI DPQAI	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mohan Sapru		Digitally signed by Mohan Sapru Date: 12/18/2024 1:31 PM EST GUID: 2024121818313		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Mark Rothmann OB DBII	Sections: 6, 15, 16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mark Rothmann			Digitally signed by Mark Rothmann Sign on behalf of Signing for Kiya Hamilton Date: 12/18/2024 4:33 PM EST GUID: 20241218213315	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Shirley Seo OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shirley Seo			Digitally signed by Shirley Seo Date: 12/18/2024 10:15 PM EST GUID: 2024121931538	

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Eileen Craig OCHEN DDLO	Sections: 1-4, 6-11, 15-25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Eileen Craig		Digitally signed by Eileen Craig Date: 12/19/2024 7:51 AM EST GUID: 20241219125138		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EILEEN M CRAIG
12/19/2024 07:52:34 AM

JOHN M SHARRETT
12/19/2024 09:04:11 AM
;

LISA B YANOFF
12/19/2024 10:46:00 AM
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