EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2025
EMA/CHMP/216788/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tryngolza

International non-proprietary name: olezarsen

Procedure No. EMEA/H/C/006477/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AESI	Adverse event of special interest
ADA	Anti-drug antibody
ADR	Adverse drug reactions
AI	autoinjector
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANCOVA	analysis of covariance
apoB-48	apolipoprotein B-48
apoC-III	apolipoprotein C-III
ASCVD	atherosclerotic cardiovascular disease
ASGPR	asialoglycoprotein receptors
ASO	antisense oligonucleotide
AUC	area under the concentration-time curve
BE	Bioequivalence
CNS	central nervous system
CSR	clinical study report
CV	Cardiovascular
CVD	cardiovascular disease
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EMA	European Medicines Agency
ER	emergency room
E-R	Exposure-response
ERA	environmental risk assessment
FCS	familial chylomicronemia syndrome
FCS-SIS	FCS Symptoms and Impacts Scale
FDA	Food and Drug Administration
FLR	Flu-like reactions
FMQ	FDA medical query
FOB	Functional Observational Battery
GalNAc3	N-acetyl galactosamine 3
GCP	Good clinical practice
GLP	Good laboratory practice
HDL	high-density lipoprotein
HED	human-equivalent dose
HR	heart rate
HTG	Hypertriglyceridemia
IDL	intermediate-density lipoprotein
IND	Investigational new drug
ISRs	Injection site reactions
ISS	Integrated summary of safety
LCRIS	Local cutaneous reactions at the injection site
LDL	low-density lipoprotein
LLOG	lower limit of quantification
LPL	lipoprotein lipase

LSM	least-squares mean
MACE	major adverse cardiovascular events
MedDRA	Medical dictionary for regulatory activities
MI	multiple imputation
MOE	Methoxyethyl
mRNA	messenger RNA
NDA	New drug application
NOAEL	No observed adverse effect level
OEAI	Other adverse events of interest
OLE	Open label extension
OTC	over the counter
PD	Pharmacodynamic
popPK	Population pharmacokinetic
popPK/PD	Population pharmacokinetic/pharmacodynamic
RBpm	respiratory breaths per minute
SAE	Severe adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SEM	standard error of the mean
sHTG	severe hypertriglyceridemia
SmPC	Summary of product's characteristics
SMQ	Standardised MedDRA queries
TC	Total cholesterol
TEAE	Treatment emergent adverse event
TG	Triglyceride
TK	Toxicokinetics
TRL	triglyceride-rich lipoprotein
UACR	Urine albumin creatinine ratio
UPCR	Urine protein creatinine ratio
ULN	Upper limit normal
US	United States
VLDL	very-low-density lipoprotein

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ionis Ireland Limited submitted on 29 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Tryngolza, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2023.

The applicant applied for the following indication:

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of familial chylomicronemia syndrome (FCS) to reduce triglycerides and the rate of acute pancreatitis events.

The final proposed indication is the following:

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tryngolza as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Tryngolza.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0041/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0041/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. Derogation(s) from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the Regulation (EC) No. 141/2000;

the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance olezarsen contained in the above medicinal product to be considered as a new active substance in comparison to volanesorsen previously authorised in the European Union as Waylivra, as the applicant claimed that olezarsen differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

1.6. Protocol assistance

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 June 2020	EMEA/H/SA/4483/1/2020/III	Elmer Schabel, Mogens Westergaard

The scientific advice pertained to the following non-clinical and clinical aspects:

EMEA/H/SA/4483/1/2020/III - Non-clinical and clinical development

- Adequacy of the proposed non-clinical development program to support initiation of the Phase 3 study and a Marketing Authorisation Application (MAA); a waiver of the fertility and embryo-foetal development study in mice, the embryo-foetal development study in rabbits, the pre- and post-natal development study in mice, and the 2-year rat carcinogenicity study.
- Adequacy of the clinical pharmacology programme to support initiation of the Phase 3 study and the MAA; a waiver of the non-clinical and clinical ADME studies; the dosage and frequency proposed in the Phase 3 study.
- The overall design of the Phase 3 study and specifically the target population, primary endpoint, secondary endpoints, and exploratory endpoints; whether a single pivotal study could be acceptable for MAA; the proposed labelling strategy; the liver chemistry, renal functioning and platelet safety monitoring planned in the proposed Phase 3 study; adequacy of the estimated size of the exposure database at the time of the MAA to support the proposed indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Larisa Gorobets Co-Rapporteur: Paolo Gasparini

The application was received by the EMA on	29 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	13 November 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 November 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 May 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 May 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tryngolza on	24 July 2025
The CHMP adopted a report on similarity of Tryngolza with Waylivra on (see Appendix on similarity)	24 July 2025
The CHMP adopted a report on derogations applicable to similar orphan products for Tryngolza on (See Appendix on derogations)	24 July 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant initially proposed the following indication:

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of familial chylomicronemia syndrome (FCS) to reduce triglycerides and the rate of acute pancreatitis events.

The final indication granted by CHMP is the following:

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive condition that is present from childhood and is characterized by severe hypertriglyceridemia (HTG), with triglyceride (TG) levels >10 mmol/L (>885 mg/dL).

The product will be given subcutaneously.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Familial chylomicronemia syndrome (FCS) is a rare, serious autosomal recessive inherited disease of lipid metabolism characterized by severely impaired lipoprotein lipase (LPL) function causing severe hypertriglyceridemia and hyperchylomicronaemia. FCS (formerly referred to as 'lipoprotein lipase deficiency' or Fredrickson hyperlipoproteinemia type I) is present in childhood to early adulthood as severe HTG, with fasting plasma TG levels >10 mmol/L (Spagnuolo et al. 2024). Patients with FCS have triglyceride (TG) levels approximately 10 to 100 times above the reference level of < 1.7 mmol/L (150 mg/dL) (Witztum et al. 2019). This rare disease has a worldwide estimated prevalence of approximately 1 to 13 per million (up to 3600 patients in the United States) (Khavandi et al. 2018; NORD 2023; Pallazola et al. 2020; Rengarajan et al. 2018; Tripathi et al. 2021; Shamsudeen et al. 2022). Prevalence rates vary depending on geographic region and whether diagnosis was based on genetic testing or clinical criteria alone.

2.1.3. Aetiology and pathogenesis

FCS is specifically due to homozygous, compound heterozygous, or double heterozygous, loss of-function, null, or nonsense, mutations in the LPL gene or in several genes that encode proteins that regulate LPL activity (e.g., apoC-II) (Blom et al. 2018; Brahm & Hegele 2015; Dron et al. 2019; Hegele et al. 2018; Surendran et al. 2012). The most frequent mutations are detected in LPL, APO C2, ApoAV, GPIHBP1, LMF1 genes (Mach F et al, 2019). To date, there are five canonical lipolysis genes implicated in FCS: LPL, GPIHBP1, APOA5, APOC2, and LMF1 (Shamsudeen et al. 2022, Hegele et al. 2022, Bashir et al. 2023). LPL is the most commonly affected gene, accounting for 60–80% of cases (Shamsudeen et al. 2022). Each gene product plays a role in the breakdown of TG-rich lipoproteins such as chylomicrons and very-low-density lipoproteins (VLDLs). Reduced LPL activity results in an ineffective clearance of TG and accumulation of chylomicrons in plasma (Falko 2018), which leads to severe hypertriglyceridemia and chylomicronemia as large chylomicrons remain in the circulation (even after prolonged fasting) (Blom et al. 2018).

Triglycerides and cholesterol esters are insoluble in plasma and are packaged as lipoprotein particles in chylomicrons and very low-density lipoproteins (VLDLs) to be transported to tissues (Huff et al. 2023). LPL is an extracellular enzyme anchored to the luminal surface of capillary endothelial walls and present mainly in heart, skeletal muscle, and adipose tissue. The normal function of LPL is to hydrolyze TG in chylomicrons and VLDLs, promoting TG-rich lipoprotein clearance from the circulation. For patients with FCS, biallelic mutations in the LPL genes lead to severely impaired LPL activity.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The manifestations of FCS are heterogeneous; however, both hypertriglyceridemia and chylomicronemia lead to a heavy burden of medical complications. The majority of symptoms are from increased levels of chylomicrons and can range from vague abdominal discomfort to multi-organ failure because of acute pancreatitis. Most patients may present in early childhood or adolescence, but they may present in later stages of life. Recurrent intermittent abdominal pain not associated with pancreatitis and fatigue are the most reported symptoms. Few other reported symptoms are bloating, asthenia, indigestion, and joint pains. Acute pancreatitis is one of the severe manifestations reported. Acute severe pancreatitis can also cause multi-organ failure and increases morbidity and mortality. It can also cause chronic pancreatitis leading to loss of exocrine function, pancreatic pseudocyst, or necrotizing pancreatitis. Patients can also present with symptoms of forgetfulness, depression, and difficulty in concentration. Further, hypertriglyceridemia can cause significant cardiovascular disease. The European Society of Cardiology/European Atherosclerosis Society in their guidelines stressed that the risk of pancreatitis is clinically significant if TGs are >10 mmol/L (880 mg/dL), particularly when occurring in association with familial chylomicronaemia, and actions to prevent acute pancreatitis are mandatory (Mach F et al, 2019). Both pancreatitis and ASCVD can result in acute events including hospitalization and/or death (Hussain et al. 2022; Liu et al. 2013; Nawaz et al. 2015; Pothoulakis et al. 2021).

Overall, the risk of acute pancreatitis increases by 3% to 4% with each incremental increase of 100 mg/dL in TG levels (dePretis et al. 2018). A TG level > 880 mg/dL has been shown to be associated with persistent chylomicronemia; therefore, the risk of acute pancreatitis is greater compared with lower TG levels for which chylomicrons are not consistently observed (Sanchez et al. 2021). This risk further increases when TG levels are > 2000 mg/dL (Berglund et al. 2012; Toth et al. 2014).

Patients with FCS have higher levels of chylomicronemia and hypertriglyceridemia than most patients with severe hypertriglyceridemia (sHTG) (Gill et al. 2021). Due to lifelong exposure to severe elevations in TGs for patients with FCS, the prevalence of pancreatitis (including recurrent pancreatitis) is reported as 10-fold higher for patients with FCS compared with patients with other forms of severe hypertriglyceridemia (Paquette et al. 2019). The prevalence of acute pancreatitis among patients with FCS may be as high as 67% (Gaudet et al. 2016) and the risk of major complications is 2 to 3-times higher compared with patients with pancreatitis who do not have hypertriglyceridemia. Recurrent episodes of acute pancreatitis may lead to the development of chronic pancreatitis, which can be fatal or lead to permanent pancreatic damage, resulting in permanent exocrine or endocrine insufficiency, including type 1-like diabetes mellitus (Gaudet et al. 2013; Kassner et al. 2015; Sisman et al. 2014).

The precise mechanism by which hypertriglyceridemia and hyperchylomicronaemia lead to pancreatitis has not been completely elucidated; two hypotheses exist. One hypothesis is that large chylomicrons lodged in pancreatic capillaries increase plasma viscosity, leading to ischemia, acidosis, trypsinogen activation, and pancreatic autodigestion (Valdivielso et al. 2014). The other hypothesis is that chylomicrons are exposed to pathologically high local concentrations of pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to trigger an inflammatory reaction, damaging pancreatic

cells and leading to emergent pancreatitis (Berglund et al. 2012; Yang et al. 2009). Treatment for patients with FCS needs to both lower TG levels and significantly reduce the accumulation of chylomicrons.

2.1.5. Management

Despite the potential life-threatening manifestations of FCS, effective treatment for this rare disease is limited. In general, the long-term management of the disease includes following an extremely restrictive low-fat diet and abstinence from alcohol; however, lifelong adherence to such a regimen is challenging and is almost never consistently achieved by most patients (Baass et al. 2020). Volanesorsen was approved by the EMA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high-risk for pancreatitis. The safety profile of volanesorsen has been well-defined. However, the risk of thrombocytopenia and bleeding requires regular platelet level monitoring. Renal toxicity has been observed, and injection site reactions have resulted in drug discontinuations. The disease and current management of the disease makes impact on the quality of life as well as other psychosocial aspects of the patient including food-related anxiety (Davidson et al. 2017). Therefore, FCS is still a disease with a high unmet medical need for effective treatments with improved safety profile.

2.2. About the product

Olezarsen is a 2'- MOE chimeric ASO covalently bound to GalNAc3, a high affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (Prakash et al. 2014). The ASO portion of olezarsen is complementary to an area within the 3'-untranslated region of the human apoC-III mRNA at base position 508-527 and binds to the mRNA by Watson and Crick base pairing. According to the applicant, due to the GalNAc conjugation, the targeted delivery of the ASO to the hepatocytes is improved compared with a currently approved volanesorsen. It allows achieving pharmacologic activity at much lower doses. Once olezarsen is taken up in tissue, the conjugate is metabolized, liberating the active apo-C-III antisense compound. As the ASO portion of olezarsen is the parent drug, volanesorsen, and is designed to bind to the human apoC-III mRNA, the hybridization (binding) of olezarsen to the cognate mRNA results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein.

According to the proposed posology, the recommended dosage of olezarsen is 80 mg administered by subcutaneous injection once monthly.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing 80 mg olezarsen (as olezarsen sodium) in 0.8 mL solution as active substance.

Other ingredients are: sodium dihydrogen phosphate (E339), disodium hydrogen phosphate (E339), sodium chloride, water for injections, sodium hydroxide (for pH adjustment) (E524), hydrochloric acid (for pH adjustment) (E507).

The product is available in in a type I glass syringe with a stainless steel staked needle, rigid needle shield, and siliconised chlorobutyl elastomer plunger stopper. The syringe is assembled into a disposable single-dose pre-filled pen (autoinjector).

2.3.2. Active substance

2.3.2.1. General Information

The active substance olezarsen is a synthetic oligonucleotide conjugated to a tri-antennary trishexylamino (GalNAc) ligand via an aminohexyl linker on the 5′ terminus. The oligonucleotide part consists of 20 nucleosides in a 5-10-5 structure with 2′-O-(2-methoxyethyl), deoxy and 2′-O-(2-methoxyethyl) sugar moieties, respectively. The backbone is formed by phosphorothioate linkages between all nucleosides and a phosphate linkage between the 5′-terminal nucleoside and the aminohexyl linker.

The chemical name of olezarsen sodium is DNA, d(P-thio) ([2′-*O*-(2-methoxyethyl)] rA-[2′-*O*-(2-methoxyethyl)] rG-[2′-*O*-(2-methoxyethyl)] m5rC-[2′-*O*-(2-methoxyethyl)] m5rU-[2′-*O*-(2-methoxyethyl)] m5rU-m5C-T-T-G-T-m5C-m5C-A-G-m5C-[2′-*O*-(2-methoxyethyl)] m5rU-[2′-*O*-(2-methoxyethyl)] m5rU-[2′-*O*-(2-methoxyethyl)] m5rU-[2′-*O*-(2-methoxyethyl)] rA-[2′-*O*-(2-methoxyethyl)]m5rU), 5′-[26-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[6-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]hexyl]amino]-3-oxopropoxy]methyl]-8,12,19-trioxo-16-oxa-7,13,20-triazahexacos-1-yl hydrogen phosphate], sodium salt (1:20) corresponding to the molecular formula $C_{296}H_{419}N_{71}O_{154}P_{20}S_{19}Na_{20}$ (sodium salt).

It has a relative molecular mass of 9124.48 Da (sodium salt) and the following structure:

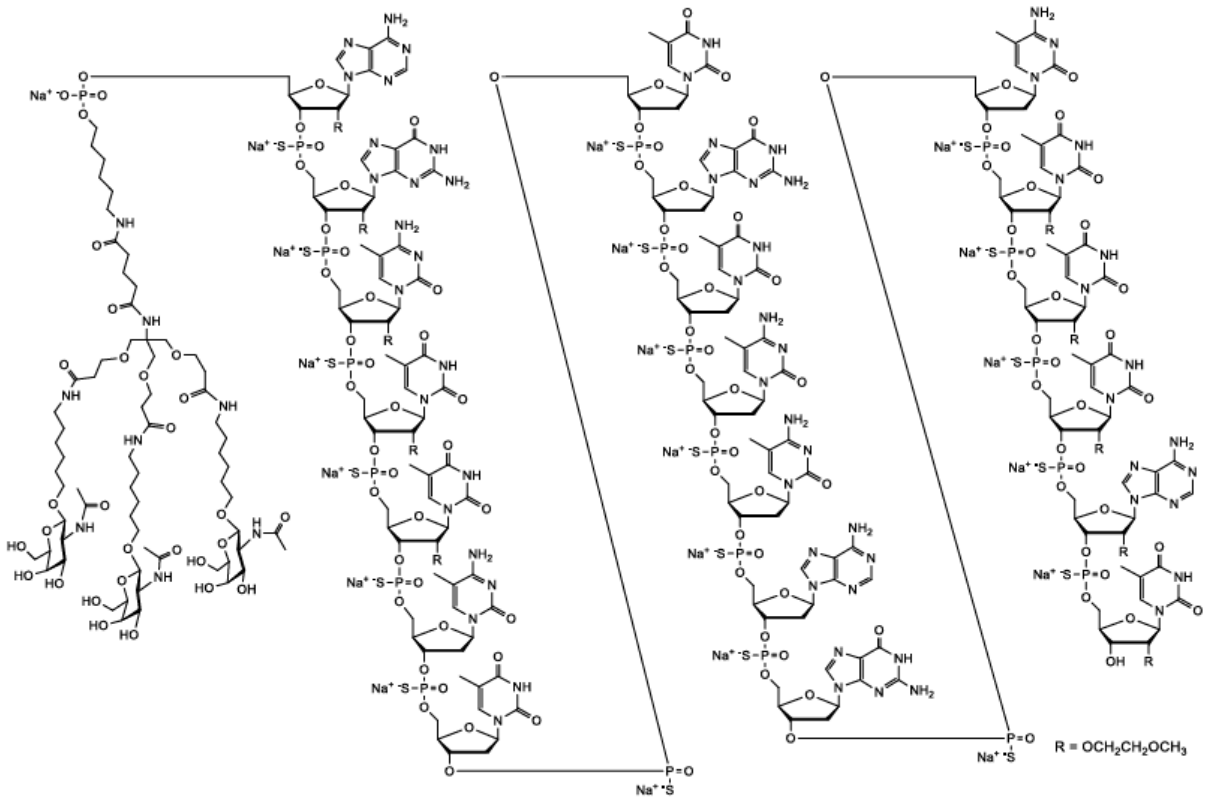


Figure 1: active substance structure

The active substance is a hygroscopic white to yellow solid freely soluble in water.

The absolute configuration of each 2-deoxy-D-ribose unit is (1*R*, 3*S*, 4*R*). The absolute configuration of each 2'-*O*-(2-methoxyethyl)-D-ribose unit is (1*R*, 2*R*, 3*R*, 4*R*). The absolute configuration of each galactosamine unit is (1*R*, 2*R*, 3*R*, 4*R*, 5*R*). The absolute configuration at each phosphorus atom of

each phosphorothioate diester is undefined; hence olezarsen sodium is a mixture of 2^{19} diastereoisomers.

Based on the discussion of the stereochemistry of the synthetic route, stereoisomeric control of the different starting materials (nucleoside phosphoramidites and GalNAc ligand (THA8), and stereochemical aspects of the phosphorothioate diester internucleotide linkages the applicant presents a reasonable rationale that the manufacture of olezarsen sodium is under stereochemical control and the active substance's stereoisomeric composition is reproducible. It is conclusively shown by analysis of DMT–on synthesis intermediates sampled after pausing the synthesis after each coupling step that the synthesis is under inherent stereo control and that olezarsen sodium is a mixture of 524288 (2^{19}) diastereoisomers with the most prevalent diastereoisomer contributing approximately 0.0018%.

The chemical structure of olezarsen sodium was elucidated by a combination of NMR spectroscopy (^{1}H, ^{13}C and ^{31}P), high resolution mass spectrometry (IP-HPLC-TOF-MS) for monoisotopic mass, failure sequence analysis and mass spectrometry fragmentation (both with IP-HPLC-TOF-MS) for sequence confirmation and elemental analysis (combustion analysis and ICP-OES and COSY/HMBC/HSQC 2D NMR. All results correspond with the expected identity and primary structure of the active substance. No defined three-dimensional structure is expected.

For physicochemical characterisation UV spectrometry for determination of an extinction coefficient, dynamic vapor sorption studies, X-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis, pH analysis of a 5% aqueous solution and solubility studies according to USP/Ph. Eur. were performed. The active substance is sufficiently characterised as hygroscopic and amorphous.

2.3.2.2. Manufacture, process controls and characterisation

The active substance is manufactured by one manufacturing site. A valid QP declaration covering the active substance manufacturing site is provided.

The active substance is synthesised via solid-phase oligonucleotide synthesis using well defined starting materials with acceptable specifications.

The commercial batch size is defined.

Solid-phase oligonucleotide synthesis is followed by chromatography and conjugation steps to yield crude conjugated intermediate. Subsequent chromatography, filtration and freeze drying steps result in the active substance olezarsen sodium. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Justified hold periods are indicated for the intermediates.

The proposed starting materials (SMs) include nucleoside phosphoramidites, MMT-Aminohexyl phosphoramidite and THA8 (5-[[tris(3-(6-(2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-galactopranosyloxy)hexylamino)-3-oxopropoxymethyl)]methyl]-amino-5-oxopentanoic acid) which represent the oligonucleotide monomers, the linker and the triantennary GalNAc ligand, respectively. All starting materials are very complex but well justified based on principles outlined in ICH Q11 and therefore considered acceptable in principle. Possible critical impurities in the nucleoside phosphoramidite SMs are described, structures shown and their fate as active substance impurity discussed. For each nucleoside phosphoramidite starting material, a specification covering appearance; color; identification, assay, purity and impurity profile by HPLC-UV-MS; water content by Karl Fischer and residual solvents by GC is presented.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. It is confirmed that the manufacturing process will be fully validated prior to commercialisation of the finished product.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Impurities in the active substance are classified into product-related impurities and process-related impurities. The product-related impurities are further sub-classified into those derived from starting materials, those formed during processing and degradation products. These are quantified using ion-pair high performance liquid chromatography with ultraviolet and mass spectrometry detection (IP-HPLC-UV-MS). As it is not possible to resolve each single impurity, a grouping strategy according to structural characteristics is applied. This is acceptable due to the generally complex impurity profile of conjugated oligonucleotides.

The product-related impurities are discussed in detail according to the abovementioned categories. The information on product-related impurities is considered acceptable and a thorough understanding of product-related impurities is demonstrated. Potential process-related impurities such as solvents, small molecules, as well as extractables and leachables from synthesis and purification resins are discussed.

An assessment for potential mutagenic impurities (PMI) according to ICH M7 covered the synthesis of the GalNAc ligand and the active substance manufacturing process. Predicted purge factors have been claimed to justify that no testing in the active substance is required which is considered acceptable.

The active substance packaging complies with European Commission Regulation (EC) No. 10/2011, as amended.

2.3.2.3. Specification

The active substance specification includes tests for appearance (visual), identification by mass (IP-HPLC-UV-MS), identification by sequence confirmation (duplex melting temperature Tm), identity and quantity of counterion (ICP-OES), assay (IP-HPLC-UV-MS), purity (IP-HPLC-UV-MS), specified oligonucleotide impurities, unspecified oligonucleotide impurities, total oligonucleotide degradation products, total oligonucleotide impurities (all by IP-HPLC-UV-MS), residual solvents (GC), bacterial endotoxins (Ph. Eur.), microbial examination (Ph. Eur.) and water content (KF).

The relevant active substance attributes are covered by this specification. Several orthogonal methods are applied to determine identity, therefore it is considered acceptable to omit a specific sequencing method. Only one purity/oligonucleotide impurities method is applied (IP-HPLC-UV-MS). This is considered acceptable since the impurities co-eluting in the LC-UV dimension can be resolved in the MS dimension and the specification limits that cover more than one impurity are sufficiently justified. Impurities are grouped according to their structures and formation mechanisms. The concept of grouping as proposed in the specification is justified, acceptable and common practice for oligonucleotides. Omission of testing for most process-related impurities is sufficiently justified and a bioassay is not required.

For the assay/purity and most impurity specifications, the acceptance criteria are based on toxicological data, batch data of five historical large-scale active substance batches, batch data from a so-called platform of the five olezarsen sodium batches and additional 30 oligonucleotides manufactured by similar processes as well as on considerations for process variability.

The applicant refers repeatedly to the use of platform data. It is fully agreed that there is a high potential for synthetic oligonucleotides to benefit from such an approach based on prior knowledge. The overall manufacturing process development is described very generally to be based on Ionis and external experience. Literature reports guided the discussion related to phosphorothioate stereochemistry. For the list of potential product-related impurities, several publications are cited in which molecules with identical nucleosides and internucleotide linkages are discussed. Additionally, Ionis-internal prior knowledge is applied. The applied HPLC-UV-MS method is well understood based on previous method validation results, which are also published, and it is reasonable to select this method for olezarsen analysis. Overall, the approach chosen to establish the initial manufacturing process and active substance control method for olezarsen based on prior knowledge is considered reasonable. Especially since additional process development, such as for example process justification experiments and olezarsen-specific method validation of the HPLC-UV-MS method, was performed. Those specification limits that were mathematically deduced form data gained by analysis of oligonucleotides other than olezarsen are each based on different so-called platforms. The explanations provided for inclusion and exclusion of batches based on the factors that influence the respective parameter are considered reasonable.

The olezarsen sodium batches are considered representative of commercial material. From the results, reasonable values were selected as specification limits. This approach is in general acceptable. The limit for certain impurities derived from starting materials is justified by a limit for the underlying starting material impurity of 0.15. Sufficiently detailed data on toxicological qualification of the oligonucleotide impurities is presented and all limits are considered toxicologically qualified. The limit for unspecified oligonucleotide impurities of NMT 1.0% is sufficiently justified as identification threshold. Similarly, as for the individual specified impurities, the limit for total oligonucleotide degradation products was set based on olezarsen-specific data and results for additional 34 oligonucleotide batches.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for eight toxicology/clinical/stability/process validation/commercial batches (including three process validation/stability/clinical/commercial batches) of the active substance is provided. The results are within the specifications and consistent from batch to batch.

2.3.2.4. Stability

Stability data from three registration batches (35% of the commercial batch scale) from the proposed manufacturer in packaging material equivalent to the commercial container closure system is provided for 36 months at long-term conditions (-20 ± 5 °C/AMB RH), 6 months at intermediate conditions (5 ± 3°C) and 3 months at accelerated conditions (30 ±2°C /65 ± 5% RH).

Stability data is also presented for the process validation batches (commercial scale) for 24 months at long term conditions (-20 ± 5 °C/AMB RH), six-months at 5 ± 3 °C and three months at 30 ± 2 °C/65 ± 5% RH. Supportive stability data for two development batches (60 and 69 months at -20 ± 5°C as well as 6 months each at 5 ± 3°C) are also provided.

Appearance, assay, purity, impurities and water content are tested at all time points. Microbial enumeration and bacterial endotoxin testing are performed at the end of the accelerated studies and yearly at long-term conditions. The provided stability protocol covers all relevant parameters as well as time points and is considered acceptable. The primary and process validation stability data results

remain within specification for all time points at all conditions. It is indicated that no significant trends are observed.

Additionally results for photostability testing and forced degradation studies are provided. The stress testing covers thermal, acid, oxidative, basic and photo stress.

Photostability studies conclusively show that no special precautions for protection from light are needed for the drug substance and forced degradation studies elucidate the main degradation products formed under the different stress conditions Mass balance the forced degradation studies substantiates that the applied assay/purity/impurities method according is stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at the recommended storage condition of -20°C±5°C in the proposed container.

2.3.3. Finished Medicinal Product

2 . 3 . 3 . 1 . Description of the product and pharmaceutical development

Tryngolza solution for injection, 80 mg, is a sterile, preservative-free and ready-to-use solution intended for subcutaneous (SC) administration. The formulation contains 100 mg/mL olezarsen free acid (105 mg/mL olezarsen sodium) in a 9.2 mM phosphate buffer at pH 7.4. Sodium chloride is added to achieve an isotonic solution. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The finished product is clear and colourless to yellow in appearance, is filled into a 1 mL staked needle glass pre-filled syringe (PFS) and is closed with a siliconized chlorobutyl elastomeric rubber plunger stopper. Each filled primary container holds 0.8 mL deliverable volume. The PFS is assembled into an autoinjector for the finished product presentation and delivers a single dose of 80 mg olezarsen.

The product is administered as a single use SC injection, once monthly. The formulation is intended only for adult patients.

The finished product and its composition are in general sufficiently described. The applicant confirmed that nitrogen is only used as a process aid and is not added to the head-space of the syringes.

The late-stage development for the finished product is based on a quality target product profile (QTPP), which is presented in the dossier. Formulation and manufacturing process development took in general into account the necessary CQAs for a sterile solution in a semi-finished syringe ("filled primary container") assembled into an autoinjector.

CPPs and IPCs for the finished product are clearly derived from and supported by the process development studies presented in the dossier.

The properties of the active substance that potentially affect drug formulation are discussed. The active ingredient is an amorphous solid that is readily soluble in water and phosphate-buffered saline with a pH of 7.4. Due to the amorphous state of olezarsen, varying dissolution rates due to polymorphs are not of concern. However, amorphous powders are generally susceptible to humidity. This is taken into consideration during compounding by determination of the content of the active substance in the concentrated bulk solution before final dilution.

Commercial formulation development started based on the clinical formulation, i.e. olezarsen solution for injection 100 mg/mL in a vial with chlorobutyl rubber stopper. For commercial formulation, the

concentration of the finished product solution was kept constant for the 0.8 mL deliverable volume (80 mg dose). Additionally, a 50 mg formulation with 62.5 mg/mL concentration was developed to allow administration of 0.8 mL deliverable volume with 50 mg dosage.

The commercial manufacturing process was then optimised. A bioequivalence study was performed to bridge the clinical (100 mg olezarsen/mL in vial, 0.8 or 0.5 mL dosing volume) and commercial presentation (100 mg/mL or 62.5 mg/mL in autoinjector, 0.8 mL dosing volume) of the finished product. The study demonstrated that administration of 80 mg and 50 mg olezarsen subcutaneously from the autoinjector met the acceptance criteria for bioequivalence to the administration of olezarsen subcutaneously from a vial via syringe.

The finished product does not contain overages. However, an overfill is required to discharge the nominal volume from the autoinjector containing the syringe. Dose accuracy has been demonstrated, results are provided in the dossier.

The manufacturing process is a common process for aqueous sterile products, which cannot be subjected to terminal sterilisation and includes the following steps: Buffer Formulation and bioburden reduction filtration, compounding and bioburden reduction filtration, double in-line sterile filtration and aseptic filling, and visual inspection. The semi-finished syringe is finally assembled into the autoinjector.

Several manufacturing process development studies were performed to evaluate compounding, bioburden reduction and sterile filtration, filling, device assembly, product contact material compatibility and processing and hold times. In addition to olezarsen-specific development studies, platform knowledge from two other oligonucleotide product formulations was leveraged for establishing the commercial finished product manufacturing process. The platform experience is applied in other sections of the dossier too, i.e. supportive platform stability data in P.8. Leveraging platform knowledge for oligonucleotide drug products is in general supported. Additionally, results from platform-independent product-specific studies (PPQ, stability) are presented to support the final finished product manufacturing process and its controls. The manufacturing process development is in general sufficiently described; no further development studies are considered necessary for this process.

The choice of sterile filtration with aseptic filling has been adequately justified in accordance with the guideline on sterilisation EMA/CHMP/CVMP/QWP/850374/2015. Moist heat sterilization applying a cycle at 121°C for 8 minutes leads to significant decrease of purity. Buffer optimisation and pH were taken into account. The degradation products increased between 3.2% to 6.2% depending on the pH of the drug product solution.

Processing and hold times were determined and qualified as part of process performance qualification.

The commercial primary container system consists of a 1mL long Type I siliconized clear glass staked needle syringe barrel closed with a siliconized chlorobutyl plunger stopper and a rigid needle shield. The components of the primary packaging are supplied ready-to-use, i.e. sterilized. The syringes are ethylene oxide sterilized in accordance with ISO 11135 and the plunger stopper gamma irradiated or steam sterilised in accordance with ISO 11137 and ISO 17665.

The semi-finished syringe is assembled into an autoinjector. Details on the autoinjector, including Notified Body Opinion, are provided in the dossier.

For the semi-finished syringe information with respect to suitability and safety has been provided. This includes testing on extractables/leachables, glass delamination assessment and testing on container closure integrity. For the accelerated leachable study, two representative antisense oligonucleotide

products are used instead of olezarsen finished product. Their suitability to act as surrogate for olezarsen finished product was sufficiently justified based on sequence similarity.

With regard to microbiological attributes, the applicant provided information that the finished product is designed to maintain sterility during assembly and storage. Compatibility studies with solvents are not required as the finished product is administered subcutaneously with no dilution.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured and primary packaged by one manufacturing site. Autoinjector assembly takes place at another site. Proof of GMP compliance for all manufacturing and testing sites has been provided.

The manufacturing process consists of seven main steps: buffer solution (vehicle) preparation, drug product solution formulation, bioburden reduction and in-line sterile filtration (immediately before filling), aseptic filling and stoppering, visual inspection, and assembly of the semi-finished syringes with the autoinjector component. Maximum processing and hold times are listed and sufficiently justified by data. The target batch size range of the drug product is defined. The in-process controls are adequate for this type of manufacturing process.

The process is considered to be a non-standard manufacturing process. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. For process validation, three consecutive batches of the primary filled container were produced, one at the lower end of the defined batch sizes and two at the upper end of the defined batch sizes . As each autoinjector unit experiences the same assembly, the process is independent of batch size. PPQ reports for manufacturing of the 80 mg (100 mg/mL) pre-filled syringes and assembly of the respective autoinjectors available. Supportive validation data for the 50 mg strength (62.5 mg/mL) is provided.

Batch release testing was performed on the finished autoinjector, except for the parameters ‘endotoxins’ and ‘sterility’. This approach was justified by demonstrating that the finished product microbial attributes are assured and maintained during final autoinjector (AI) assembly and following operations. Validation of the membrane filters was performed covering microbial retention, viability and recovery studies, and membrane compatibility. Results of media fill runs at the finished product manufacturing site sufficiently demonstrated a maximum filling time of 48 hours for the finished product solution into the syringes.

The primary container closure system for the finished product comprises of a 1 mL Long staked needle syringe barrel and a chlorobutyl elastomeric plunger stopper. The filled primary container is assembled into an autoinjector that is labelled and packaged in a carton to secure the autoinjector and protect it from light. The syringe and the plunger stopper are supplied ready to use, i.e. sterile. Sufficient information of the sterilization of the primary packaging components have been provided.

The glass syringe and the plunger stopper as well as the silicone oil used as lubricant for both components comply with the respective Ph. Eur. monographs, i.e. Ph. Eur. 3.2.1 ‘Glass containers for pharmaceutical use’, Ph. Eur. 3.2.9 ‘Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders’ and Ph. Eur. 3.1.8 ‘Silicone oil used as a lubricant’. Sufficient specifications for the glass syringe, the plunger stopper and the medical device part of the drug product are provided and acceptable.

Further details on the medical device part of the drug product, the Notified Body Opinion Report, and the Human Factors Report are included in Module 3.2.R.

2.3.3.3. Product specification

The finished product specifications includes appropriate tests for this kind of dosage form; appearance (visual), degree of coloration (Ph. Eur.), clarity and degree of opalescence (Ph. Eur.), identification by sequence confirmation (duplex melting temperature Tm), identification by mass (IP-HPLC-UV-MS), assay, purity, specified oligonucleotide degradation products, unspecified oligonucleotide degradation products, total oligonucleotide degradation products (all by IP-HPLC-UV-MS), pH (Ph. Eur.), osmolality (USP), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), container closure integrity (vapor pressure), uniformity of dosage units (Ph. Eur.), activation force, injection time (Mechanical Force and Time Analysis ISO), delivered volume (USP).

The shelf-life specification includes assay, purity and impurities, the safety tests sterility, endotoxins, container closure integrity and particulate matter, the general tests appearance, degree of coloration and clarity/opalescence and pH as well as the autoinjector specific tests on activation force, injection time and delivered volume. The acceptance criteria for release and shelf-life are identical.

Because physicochemical CQA are not impacted by the assembly process, and to permit operational flexibility, physicochemical release testing may be performed on either the bulk prefilled syringe or on the assembled autoinjector. Release testing for microbial attributes will be performed on the PFS only and for functional attributes on the AI only. For stability testing, all parameters are tested on the AI.

Deamination, elemental impurities and autoinjector primary function requirements are not included in the release and shelf-life specification of the finished product. Primary stability data show no significant change in purity levels or deamination. Elemental impurities were found to be well below 30% of the respective PDE values. Additional functional testing (cap removal force, needle length, and needle cover lockout displacement) was conducted during development for design and performance verification of the autoinjector. Therefore, omission of those attributes in the specification is acceptable.

The finished product acceptance criteria are chosen based on historical batch data, including development batches or are controlled to the stated compendial limits. The chosen limits are considered sufficiently justified and acceptable. The release and shelf-life assay limits have been revised from 90.0-110.0% to 92.0-108.0%. The justification for this range is acceptable. Limits for specified degradation products are covered by qualified toxicology levels.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for clinical batches and batches of the finished product in autoinjectors manufactured by the commercial manufacturer are provided. In addition, batch analysis data of clinical batches in vial and preclinical batches are presented. All batch results are within specifications.The physicochemical and functional release tests for the three process validation batches were carried out using assembled autoinjectors, except for the tests for sterility and endotoxin that were carried out using the respective primary filled containers.

Concerning degradation products the applicant included single and total degradation products in the release and shelf-life specifications. In accordance with ICH Q3D guidance, elemental impurities have been evaluated based on a risk assessment of the contribution from the individual components of the finished product. As the levels of elemental impurities in the finished product are below the ICH Q3D control threshold (30% of the respective PDE), no testing for elemental impurities is performed for the finished product.

A risk evaluation on potential nitrosamine impurities in the active substance and in the finished product was carried out considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

2.3.3.4. Stability of the product

Stability data from three batches of finished product stored for up to 36 months under long term conditions (5 ± 3°C/Ambient RH with transitioning of the samples to 30°C/75% RH for 6 weeks prior to a time point) and for up to 6 months under accelerated conditions (25 ± 2°C/60 ± 5% RH) according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Both steam and gamma sterilized plunger stoppers are used. The applicant presents a bracketing approach with stability data from primary and PPQ batches to cover both scenarios.

Samples were tested in line with the finished product shelf-life specification. A test on deamination products is part of the stability protocol but is not included in the shelf-life specification. Instead of sterility, CCIT is performed during stability testing. Under long-term and accelerated storage conditions, no significant changes were observed in any of the attributes.

Additional 72 months supportive stability data at the long-term storage condition (5 ± 3°C) and 6 months data at accelerated storage condition (25 ± 2°C) for one clinical batch presented in a glass vial is given is provided, showing little to no change in the finished product characteristics.

As it is demonstrated that long-term and accelerated results on stability indicating parameters show little change over time, the 12 months extrapolation is acceptable and the shelf life of 48 months at the long-term storage condition of 5 ± 3°C can be granted.

The confirmatory photostability study according to guideline ICH Q1B with autoinjectors assembled with filled primary containers and without paperboard carton did not point to light sensitivity. But since photolytic degradation of olezarsen active substance and bulk finished product solution was observed during forced degradation studies the applicant nevertheless proposed that the finished product is stored protected from light, in opaque cartons. The stability data support the proposed allowance for the end-user to store the finished product for up to 6 weeks at a temperature less than 30°C. To guarantee the respect of this time limit outside the refrigerator, it was requested to introduce a section on the outer packaging where the start date (out of refrigerator) would be written, in order to calculate the 6 weeks allowed. The applicant agreed and added the text "Discard after" to the outer packaging. Moreover, additional instructions to fill this section with the correct calculation of the expiry date have been provided in the PL (section 5) and SmPC (instruction for use), when Tryngolza is stored outside the refrigerator.

In conclusion, based on available stability data, the proposed shelf-life of 4 years when stored in a refrigerator (2 °C – 8 °C) in the original package in order to protect from light, as stated in the SmPC (section 6.3), is acceptable. Tryngolza can be stored in the original package outside the refrigerator (up to 30 °C) for up to 6 weeks. If not used within the 6 weeks, it should be discarded.

2.3.3.5. Post approval change management protocol(s)

Not applicable.

2.3.3.6. Medical device issues

The dossier contains sufficient information on the autoinjector covering the description of the device parts and its components, design standards and guidance for development, design verification and changes, biocompatibility, human factors engineering, risk management and a manufacturing summary.

In addition, a Notified Body Opinion for the autoinjector has been included confirming compliance of the device incorporated into an integral drug-device combination product with Annex I (General Safety and Performance Requirements) of Regulation (EU) 2017/745 on Medical Devices.

The information on the autoinjector is largely considered sufficient. It was confirmed that the submitted Notified Body Opinion also covers the design changes of the AI post-design verification.

2.3.3.7. Adventitious agents

A material of animal origin is used in the manufacture one of the active substance starting materials. It is concluded that the material is acceptable for use because it complies with the requirements in EMA/410/01 Rev. 3 as a negligible risk for transmitting animal spongiform encephalopathy agents per the controls at place through the qualified vendor. An adequate risk assessment on viral safety has been provided.

2.3.3.8. GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Tryngolza contains olezarsen as active substance which is a 2'-MOE chimeric ASO covalently bound to $GalNAc_3$, a high affinity ligand for the hepatocyte-specific asialoglycoprotein receptor. Olezarsen is indicated as an adjunct to diet to reduce TGs in adults with FCS. Tryngolza Solution for Injection is a sterile, single-dose, ready-to-use parenteral solution of olezarsen intended for monthly subcutaneous (SC) administration.

The nonclinical testing strategy for olezarsen followed a development pathway typical for a new drug product and was consistent with existing regulatory guidance.

Non-clinical studies were mainly conducted in monkeys, except for some cases where a mouse specific surrogate inhibitor of apoC-III mRNA was used for pharmacodynamic (PD) and repeated-dose toxicity studies in mouse.

2.4.2. Pharmacology

Olezarsen was evaluated *in vitro* in primary hepatocytes, transgenic mice expressing human apoC-III, wild-type (normal) CD-1 mice and cynomolgus monkeys.

2.4.2.1. Primary pharmacodynamic studies

Primary pharmacodynamic *in vitro* studies. Study (No. 23-133f) shows that olezarsen (the sequence 5'-AGCTTCTTGTCCAGCTTTAT-3') matches the human apoC-III mRNA and targets a site that is free of meaningful sequence variation. In human cells in culture olezarsen showed selectivity for the human apoC-III mRNA. The *in silico* predicted off-targets were either not expressed in liver or kidney cortex or were not reduced significantly at any concentration tested. The single nucleotide polymorphism in *in silico* analysis according to currently available datasets, revealed no high frequency variants (i.e., variants with global or population-specific minor allele frequency (MAF) > 0.01) within the binding region of olezarsen. The MAF of 7 variants was < 6.0E-04.

In vitro Study (No. 20-1d52) evaluating olezarsen activity on apoC-III mRNA in human hepatocytes evidenced concentration-dependent 82% reduction with an IC_{50} of 0.18 μM.

In two *in vitro* studies (No. 23-0f53 and 20-190a) with hepatocytes obtained from human apoC-III transgenic mice, olezarsen produced concentration-dependent apoC-III reductions with an IC_{50} and maximal efficacy of 0.012 μM and 89% knockdown, respectively.

Primary pharmacodynamic *in vivo* studies. Olezarsen in transgenic mice that express human apoC-III (Study EX/3979_73, 23-144a) demonstrated potent dose-responsive reductions in liver apoC-III mRNA, plasma apoC-III protein, and plasma TG, with up to 87% reductions in plasma apoC-III and plasma TG observed. When compared to volanesorsen, the potency (ED_{50}) of olezarsen was 13-fold more potent in reducing liver C-III, plasma apoC-III and plasma TG. Of note, olezarsen is the GalNAc conjugated version of volanesorsen.

Study (EX/3980_166) with the Mouse Surrogate ApoC-III ASO in CD-1 Mice evidenced that olezarsen after 6 weeks of treatment, liver apoC-III mRNA expression and plasma TG concentrations reduced by 88% and 76% relative to control saline-treated mice, respectively.

Olezarsen was evaluated in lean cynomolgus monkeys (Study 678354-AS02) to determine the changes in apoC-III following up to 39-weeks of treatment. After 13 weeks of olezarsen treatment, liver apoC-III mRNA expression was dose-dependently reduced by 77, 85, 83 and 89% in the 2, 6, 12 and 30 mg/kg/wk dose groups, respectively. In this study apoC-III reductions had minimal effect to reduce plasma TG. Presumably, the extent of the decrease in circulating triglycerides induced by olezarsen, is likely dependent on the level of plasma triglycerides at baseline. Near complete recovery of liver or plasma apoC-III was observed following 26 weeks after cessation of olezarsen treatment.

The PD *in vitro* and *in vivo* studies support a potential therapeutic benefit of olezarsen in human. The text of SmPC section 5.1 "Mechanism of action" corresponds to non-clinical study's findings.

2.4.2.2. Secondary pharmacodynamic studies

The applicant did not perform non-clinical secondary pharmacodynamics studies with olezarsen. Argumentation that ASOs are highly specific to their target sequences and secondary off-target actions are expected to be minimal, is acceptable.

2.4.2.3. Safety pharmacology programme

No hERG current blocking by olezarsen (30 and 300 μM) was observed. The IC_{50} for the inhibitory effect of ISIS 678354 on hERG potassium current was not calculated but was estimated to be greater than 300 μM. Study 678354-AS03 evaluated arterial blood pressure (ABP), heart rate (HR), respiratory breaths per minute (RBpm), core body temperature (BT), 2-lead electrocardiogram (ECG) parameters and arterial blood gases were evaluated in surgically implanted telemetered monkeys following a single administration of olezarsen at 12 and 30 mg/kg. There were no test article-related changes on cardiovascular (CV) or respiratory function. The potential effect of olezarsen on the central nervous system (CNS) was evaluated in conscious non-telemetered monkeys by Functional Observational Battery (FOB) assessment (Study 678354-AS03) using 12 and 30 mg/kg doses. No FOB changes were observed in monkeys up to 30 mg/kg olezarsen. Bridging data from toxicology studies in mice and monkeys did not reveal the test article's impact on renal function, based on no changes of serum chemistry and/or urinalysis parameters. The data provided supports the proposed posology of olezarsen as safe.

2.4.2.4. Pharmacodynamic drug interactions

The applicant did not perform dedicated non-clinical PD DDI studies with olezarsen. Omission of this kind of studies is acceptable knowing that olezarsen inhibit translation of the apoC-III gene by specifically binding to its mRNA and promoting its degradation, the sequence-driven specificity of this binding greatly reduces the likelihood of pharmacological action on another gene product. *In vitro* drug-drug interaction studies were performed to evaluate the potential for involvement in CYP, transporter-, or plasma protein binding-mediated drug-drug interactions. Possible co-medication issues are considered in clinical part of the dossier and SPC 4.5 section.

2.4.3. Pharmacokinetics

To evaluate PK characteristics and olezarsen disposition in animal studies the applicant used relevant validated bioanalytical methods. The validation reports are presented in the dossier and show acceptable precision, accuracy, sensitivity, as well as reproducibility of the assays. Part of assays were validated at in-house level and confirmation of their suitability are presented in individual study report of the dossier.

The pharmacokinetics were studied in mice and monkeys. Monkey is considered the most relevant species to humans based on the general pharmacokinetic behaviour of olezarsen (T_{max}, plasma AUC, $t_{1/2}$, and clearance).

Absorption. For the exposure of olezarsen in mice (GLP Study No. 678354-APK01) were characteristic quick absorption (T_{max} - 0.5 to 1.0 hour), comparable Cmax values on Day 42 relative to Day 1 for both the 2 and 10 mg/kg dose levels, with moderate accumulation in AUC following repeat dosing on Day 42 and plasma disposition to be multi-phasic with rapid clearance, corresponding to extensive uptake in liver and kidney tissue.

The nonclinical plasma PK of olezarsen in the 39week repeat-dose toxicity study in monkey (GLP Study No. 678354AS02) elucidated that the test article was rapidly absorbed into the systemic circulation after SC administration (T_{max} - 1 to 4 hours). Following SC doses, mean peak exposure (Cmax) and total plasma exposure ($AUC_{0\text{-}48h}$) were dose dependent in animals without ADAs. Unconjugated olezarsen concentrations in kidney cortex increased nearly dose-proportionally and liver concentrations increased less than proportionally to dose, suggesting saturation of liver uptake at higher dose levels. This explains the initial rapid distribution phase from plasma that was followed by a much slower elimination phase with a terminal elimination half-life of 29.7 and 30.5 days in Group 4 (12 mg/kg) and Group 5 (30 mg/kg) recovery animals, respectively, following 13 or 39 weeks of olezarsen treatment. In monkeys the anti-olezarsen antibodies were detected in 16.7% to 87.5% of animals, depending on study type. The Cmax and AUC0-48h following 39 weeks of treatment were 2- to 4-fold higher in ADAs positive animals compared to negative animals. The presence of anti-olezarsen antibodies also increased plasma trough concentrations.

The bridging from toxicology studies with olezarsen using higher than clinically relevant doses confirm continuous and generally dose-dependent exposure to olezarsen in the repeat-dose SC mouse and monkey toxicity studies. Assays data show that olezarsen is rapidly cleared from plasma and distributed in tissues with prevalence of liver and kidney. Intake into hepatocytes occurs trough asialoglycoprotein receptors (ASGPR). Then, olezarsen is cleared slowly with elimination half-lives ranging from 3 to 4 weeks in monkey kidney cortex, 2.5 to 4 weeks in monkey liver, a similar range as that in plasma (3.5 to 4 weeks), justifying more prolonged dosing, i.e., monthly.

Distribution of olezarsen has been characterized by toxicology studies using mice and monkeys. Results from 13-week and 26-week repeat-dose toxicity studies (Study No. 678354-AS01 and No. 678354 AS04 GLP) in mice evidence that the concentrations of unconjugated ISIS 678354 were dose-dependent and appeared to increase dose-proportionally in liver and greater than dose-proportionally in kidney throughout the administered dose range.

In monkey's organism (Study No. 678354-AS02) unconjugated ISIS 678354 concentrations in kidney cortex increased nearly dose-proportionally and liver concentrations increased less than proportionally to dose, suggesting saturation of liver uptake at higher dose levels. Tissue concentrations decreased over time in a monophasic pattern in monkeys, with half-life in the range of 22.6 to 30.8 days in kidney cortex and 17.1 to 29.3 days in liver, a similar range as that in plasma (24.4 to 30.5 days). This suggests that the terminal elimination from plasma likely represents equilibrium between tissues and circulating drug due to slow elimination from tissues.

The applicant had not conducted radiolabeled investigation with test article arguing that such study (Study No. 304801-APK02) in rats with the unconjugated version of olezarsen, volanesorsen (also known as ISIS 304801) had been performed. Results showed that the kidneys contained the highest levels of radioactivity (>10-fold compared to the liver) at all time-points evaluated, followed by the injection site, liver, mesenteric lymph nodes and bone marrow. Tissues that contained moderate levels of radioactivity were thyroid, spleen, bone, pancreas, walls of the gastrointestinal tract, adrenals,

testes, skin, prostate and peri-renal fat. Very little radioactivity was associated with the brain and spinal cord.

In relation to findings in the dedicated olezarsen and volanesorsen distribution studies and observed predominance of olezarsen uptake in kidney and other organs that are not target organs, possible safety issues could arise, particularly with dose increase (relation with prolonged persistence and signals from toxicology studies), particularly after long term administration of the test article in humans.

The test article was highly bound (≥98.65%) to whole plasma proteins in human, cynomolgus monkey, and mouse blood plasma at 5 and 150 µg/mL concentrations tested (Study No. 678354-IS04).

Assay (No. 678354-IS11) evaluating the blood to plasma ratio (0.488 and 0.980) evidenced that olezarsen distributes mostly in the plasma compartment for monkey and human.

The applicant conducted study (No. 678354-AS08 GLP) to evaluate the potential effects of olezarsen in reproductive animals in CD-1 mice and uptake of the test article in liver and kidney. Thus, concentrations in liver and kidney were generally dose-dependent over the dose range of 5 to 20 mg/kg in parental male and female with lover quantities in female mice.

Biotransformation. The applicant performed assays elucidating the fate of olezarsen in mice, monkeys and human liver, kidney, plasma, and urine using in-house, non-validated analytical methods.

In mice plasma (study No. 678354-APK01) at the pre-dose time point on Day 42 in Group 2 (10 mg/kg) the unconjugated form was the only quantifiable full-length ASO species at that timepoint accounting for 100%. At the 1hour post-dose timepoint on Day 42, the fully conjugated form was the most abundant full length ASO species (81.7%) and 10.9%, 3.59%, and 3.11% of olezarsen with 1, 2, or 3 GalNAc sugar deletions, respectively, in Group 2. After evaluation of linker-related metabolism 2 metabolites were quantified (M8 and M12) and 8 detected. They composed < 6% of parent drug concentrations.

The unconjugated olezarsen was the major component observed in mouse urine samples. In this matrix were quantified 2 metabolites (M8 and M12) and 9 detected.

In mice (Study No. 678354-AS01) kidney and liver unconjugated olezarsen ranged approximately from 78% to 85% of the total oligonucleotide present with chain-shortened oligonucleotide metabolite detected at < 1% to < 7% level.

In monkey plasma (Study No. 678354AS02) prevailed intact olezarsen at the 2-hour time point, while the unconjugated form was the most abundant full-length ASO species in trough samples (168 hours post-dose). At the 2-hour time point, the full-length oligonucleotides accounted for > 94% of total oligonucleotides, while some chain-shortened metabolites were observed, and each accounted for < 6% of the total oligonucleotides detected. At Day 91 pre-dose, total full-length ASO species and N-6 metabolites accounted for approximately 67% and 20%, respectively. In monkey kidney cortex and liver samples unconjugated olezarsen, was the most abundant oligonucleotide species and accounted for approximately 95% and 91%, respectively. Chain-shortened metabolites of unconjugated olezarsen were detected that ranged from < 1% to < 2% of the total peak areas in kidney cortex and < 1% to < 4% of the total peak areas in liver. Ten (10) linker-related metabolites (i.e., M4 through M12 and M14) were detectable in monkey plasma but the metabolite concentrations are substantially lower compared to parent drug concentrations (< 1% of parent drug in monkey). By 24 hours, concentrations of these metabolites generally decreased by over 2- to 10-fold. The minimal concentrations of linker-related metabolites observed in plasma over time suggest that linker-related metabolites were minimally released to circulation and subsequently rapidly excreted to urine. There

were no urine samples for analysis from monkey. Clarification for not performing urine sample testing in monkeys was provided by the applicant. Urinary collection was indeed prohibited by the animal welfare regulation from Environment and Consumer Protection (LANUV) at the in-life animal facility. Therefore, literature data were given on both urinary excretion and metabolite profiles of this class of compound, being similar across monkey, rat and human. Minimal renal excretion and metabolites of (GalNAc)-conjugated ASOs were also described for monkeys, which are known to be consistent with those observed in humans.

In human plasma (Study No. ISIS 678354-CS1) at the 2 hours post-dose only fully conjugated olezarsen was detected. In urine, comparably, the unchanged olezarsen was the major oligonucleotide component. There were reported 8 linker-related metabolites, the highest levels typically presented at the 2-hour time point with very small concentrations (< 1% of parent drug in human plasma). Concentrations of linker-related metabolites in urine appeared substantially higher than in plasma with 11 metabolites detected.

Overall, the biotransformation of olezarsen is related to the endo- and exo- nuclease-mediated hydrolysis to form chain-shortened metabolites that are rapidly eliminated even after repeated dose administrations.

Excretion. The excretion characteristics of olezarsen are obtained from study in CD1 (ICR) male mice (Study No. 678354-APK01). In pooled urine only < 1% of full-length ASO (encompassing fully conjugated, partially conjugated (olezarsen with 1, 2, or 3 GalNAc sugar deletions), and unconjugated olezarsen) was recovered within the first 48 hours following SC dose administration. No excretion in feces assays with olezarsen were conducted.

As olezarsen is pro-drug and is rapidly metabolized to volanesorsen (i.e., unconjugated olezarsen), the applicant relays on a radio-labelled PK study in rat (Study No. 304801-APK02). Following a single subcutaneous injection of 5 mg/kg formulated [^{3}H]-volanesorsen to male rats, excretion of [^{3}H]-volanesorsen-related radioactive residues in excreta was slow and occurred mainly via urinary excretion, and to a lesser extent fecal elimination, i.e., only approximately 14%, 19%, and 48% of administered dose was eliminated in the excreta within the first 24 hours, 168 hours, and 56 days, respectively.

Data from literature (Shemesh et al. 2016) with another GalNAc-conjugated ASO and the same linker structure, showed that in rat the THA linker was extensively metabolized by oxidation, with approximately 25% of administered radio-labelled dose being recovered in urine and 71% in feces in 24 hours achieving near complete recovery (Shemesh et al. 2016).

Pharmacokinetic drug interactions. The olezarsen as oligonucleotide is not substrate for cytochromes, thus, its PK is unlikely to be impacted by other drugs that are CYP inhibitors or inducers.

DDI studies with cryopreserved human primary hepatocytes showed that olezarsen not significantly induced CYP1A2, CYP2B6, or CYP3A4 at either the mRNA or enzyme activity level (Study No. 678354-IS07) and not inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) (Study No. 678354-IS10). From Study No. 678354-IS08 is elucidated that olezarsen is not a substrate or inhibitor of major drug transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP) at concentrations of 10 µM and 100 µM. No plasma protein binding displacement *in vitro* was observed between olezarsen and other highly plasma protein-bound drugs, such as warfarin and ibuprofen (Study No. 678354-IS06). The degree of olezarsen, warfarin and ibuprofen bound to plasma proteins *in vitro* was determined to be ≥ 98.53%, ≥ 99.65% and ≥ 99.50% respectively, and the percent displacement of this binding was negligible.

No specific other PK studies with olezarsen were performed.

2.4.4. Toxicology

The batches of olezarsen drug substance used in the toxicology and safety pharmacology studies were the same as those used in the clinical trials and are aligned with the proposed commercial drug substance and product. In the safety pharmacology studies, batch CA678354-001 was tested on cynomolgus monkeys and HEK293 cells. For repeated-dose toxicity studies, this same batch was tested on mice and cynomolgus monkeys. The genotoxicity studies involved CD-1 mice, *S. typhimurium* and *E. coli* bacteria, and Chinese hamster lung cells, all using batch CA678354-001. The reproductive and developmental toxicity studies used batch CA678354-002 in CD-1 mice. In other toxicity studies, specifically for impurity qualification, batch CA678354-002 was also tested in CD-1 mice. The data across these studies show consistency in batch use across non-clinical and clinical studies.

2.4.4.1. Single dose toxicity

In accordance with the amended guidance on single-dose toxicity (EMA/CHMP/81714/2010), it is acknowledged that acute toxicity information can be derived from dose-escalation studies or short-duration dose-ranging studies that establish the maximum tolerated dose (MTD) in general toxicity test species. Based on this approach, no specific acute toxicity studies have been conducted with olezarsen. However, the safety profile has been evaluated through alternative studies. Notably, a mouse micronucleus study (Study No. 678354-AS05) involved administering large doses of olezarsen (up to 2000 mg/kg, administered twice), providing relevant acute exposure data. Additionally, monkey toxicology studies have been designed to assess acute toxicities, further contributing to the understanding of olezarsen's acute toxicity profile.

According to the ICH M3 (R2) guidelines, acute toxicity information can be obtained from appropriately conducted dose-escalation studies or short-duration dose-ranging studies that define an MTD in general toxicity test species. When acute toxicity information is available from any study, separate single-dose studies are not recommended.

A micronucleus test, even at a dose of 2000 mg/kg, is generally insufficient to fully replace the need for single-dose toxicity studies. While the micronucleus test is valuable for assessing genotoxicity, it is not designed to evaluate the full range of toxicological endpoints, such as systemic toxicity, organ-specific toxicity, or mortality, which are typically the focus of single-dose toxicity studies. In this study, the MTD was not reached, as no observable toxicological effects were noted at the highest dose of 2000 mg/kg. The lack of an MTD limits the conclusions regarding the potential acute high-dose effects of olezarsen, and this study does not fully satisfy the requirement for MTD determination.

Furthermore, the monkey toxicology studies have been designed to assess acute toxicities. The rationale provided by the applicant is not entirely agreed with, as micronucleus studies are not designed to assess single dose toxicity. However, acute toxicity obtained from the repeat dose toxicity study in monkey is accepted.

2.4.4.2. Repeat dose toxicity

Repeat-dose toxicology studies for olezarsen included sub-chronic (13-week with a 13-week recovery) and chronic (26- or 39-week with a 13- or 26-week recovery) toxicity studies conducted in CD-1 mice and cynomolgus monkeys. In these studies, animals received weekly subcutaneous (SC) doses of 2, 6, and 24 mg/kg/week or 2, 6, 12, and 30 mg/kg/week in the 13-week mouse and monkey studies, respectively. In the chronic toxicity studies, mice were administered 2, 6, and 20 mg/kg/week for 26 weeks, while monkeys received 2, 6, and 12 mg/kg/week for 39 weeks. A mouse-specific apoC-III

inhibitor (ISIS 838707) was included in the chronic mouse study at 6 mg/kg/week. The reversibility of toxicity was evaluated in all repeated-dose studies.

Pharmacokinetics in plasma and tissues were assessed as part of the toxicity evaluation. Data were derived from the 13- and 26-week mouse studies and the 13- and 39-week monkey studies. In mice that received 24 mg/kg/week, haematological changes included reversible reductions in red blood cell mass and increased neutrophil counts in males. Clinical chemistry findings revealed ALT and AST increases at doses ≥6 mg/kg/week, associated with liver hypertrophy. Organ weight changes included increased liver and spleen weights at doses ≥6 mg/kg/week. Microscopic findings included vacuolated macrophages in various tissues, liver hypertrophy, and splenic red pulp hypercellularity at doses ≥6 mg/kg/week. Kidney effects were observed at 24 mg/kg/week, with basophilic granules in tubular cells, although partial recovery was noted during the recovery phase.

Similar reversibility was observed in monkeys, particularly at 20 mg/kg/week. Findings included organ weight changes in the liver, spleen, and kidneys, as well as microscopic findings such as vacuolated macrophages in tissues. In both species, toxicokinetic analysis primarily focused on tissue distribution, with standard plasma pharmacokinetic parameters like C_{max} and AUC not being a key focus. In monkeys, doses ≥12 mg/kg/week were associated with mild reversible increases in ALT and AST without significant liver pathology, as well as slight decreases in albumin levels.

Tissue-specific pharmacokinetics revealed that drug accumulation in organs, particularly the liver and kidneys, was dose-dependent, with steady-state concentrations achieved after 13 weeks of dosing. Microscopic changes, such as hepatocellular hypertrophy and Kupffer cell activation, were observed in the liver at higher doses, along with basophilic granules in the kidney. Immunologically, slight increases in IgM were noted at doses ≥12 mg/kg/week, and anti-drug antibodies (ADA) were detected in up to 62.5% of animals, but this did not significantly affect drug exposure or efficacy.

During the recovery phase, partial or complete resolution of findings in the liver, spleen, and kidneys was noted, with reduced severity of organ weight changes and diminished microscopic findings. Overall, the toxic effects observed were generally reversible, with notable recovery in most parameters, highlighting the transient nature of the drug-induced effects at the evaluated doses.

Based on the comprehensive data provided from the repeat-dose toxicology studies for olezarsen in CD-1 mice and cynomolgus monkeys, including sub-chronic and chronic exposure paradigms, the following observations and assessments can be made in alignment with the ICH M3(R2) guidelines for non-clinical safety studies:

The studies were well-structured, employing both rodent and non-rodent species with dose regimens and durations that are relevant to support the planned duration of human clinical trials. This is in accordance with regulatory expectations where repeated-dose toxicity studies in two mammalian species (one non-rodent) should support the clinical trial durations.

Doses ranged from 2 to 30 mg/kg/week in monkeys and 2 to 24 mg/kg/week in mice, with higher doses providing insight into potential adverse effects and systemic exposure levels. The study design facilitated the evaluation of dose-dependency in toxicological response, which is critical for identifying NOAEL (No Observed Adverse Effect Level) and establishing safety margins.

The key findings across these studies indicate olezarsen was generally well tolerated at the lower dose ranges. Observed toxicities, including changes in organ weights, haematology, and clinical chemistry parameters, were dose-dependent and largely reversible, which supports the contention of manageable toxicity profiles at therapeutic dose levels.

The studies on olezarsen reveal a dose-dependent toxicity profile where lower doses up to 6 mg/kg/week are better tolerated, with minimal and reversible effects. Higher doses, particularly from

the monkey study starting at 12 mg/kg/week, show more severe changes that require close monitoring. The recovery periods included in these studies highlight the reversibility of olezarsen's effects, underscoring its potential for safe use in long-term therapy when doses are carefully managed. This data is essential for understanding the drug’s behaviour in chronic administration scenarios, with most parameters showing full or partial reversibility.

The integration of toxicokinetic data provides a robust basis for comparing systemic exposures in animal models to those anticipated in humans, ensuring that the animal models used are predictive of human outcomes. This is in line with ICH M3(R2) guidelines recommending the availability of such data prior to long-term human exposure. These values reflect a progressive increase in both C_{max} and AUC with dose escalation. The substantial rise in these parameters at higher doses correlates with the increased toxicological findings observed, particularly at the 30 mg/kg/week dose. The intermediate dose (12 mg/kg/week) also shows a significant increase in C_{max} and AUC compared to the NOAEL (6 mg/kg/week), indicating a dose-dependent increase in systemic exposure and potential for heightened toxic effects.

In the mouse studies, toxicokinetics (TK) were evaluated primarily through tissue concentration analyses, as plasma pharmacokinetic parameters like C_{max} and AUC were not directly measured. Tissue distribution of olezarsen was observed to increase dose-dependently in key organs like the liver and kidneys, with higher tissue accumulation at the highest doses (20-24 mg/kg/week). This accumulation also correlated with some of the histopathological findings in these organs, suggesting tissue retention of the drug may be related to observed toxic effects.

In the monkey studies, tissue TK similarly showed dose-dependent increases in liver and kidney concentrations of olezarsen. These findings paralleled the plasma pharmacokinetic data, with both tissue and systemic exposure rising substantially with higher doses. The tissue concentrations in the liver and kidneys were found to be much higher at 12 and 30 mg/kg/week doses compared to the lower doses, reinforcing the correlation between systemic exposure and the severity of toxicological findings at these higher dose levels. The persistence of the drug in tissues during the recovery phase also suggested a slow clearance from tissues, which could be important in understanding the long-term safety profile of olezarsen.

All repeated-dose toxicity studies, including 678354-AS01, 678354-AS02, and 678354-AS04, were conducted under Good Laboratory Practice (GLP) conditions. However, several specific analyses were labelled as non-GLP. These include the Cytokine/Chemokine analysis, Immunoglobulin (IgG/IgM) analysis, and Tissues for mRNA analysis (678354-AS04). Additionally, complement C3 and Bb: blood schedule and sampling, target plasma protein analysis (group 1-5 only), possible polymerase chain reaction analysis for plasmodium (group 1-5 only) (678354-AS02), and potential Cytokine/Chemokine analysis (group 1-4) as well as faeces collection for potential THA linker analysis (678354-AS01), were labelled as non-GLP.

Overall, the design, duration, methodology, and number of repeated-dose studies, as well as the number of animals tested, are sufficient to characterize the toxicological profile of olezarsen. Also, GLP compliance is required for analyses that directly contribute to the study's primary objectives, but non-GLP compliant data can be accepted for exploratory or supplementary endpoints. In this case, the provided non-GLP-compliant data can be accepted for exploratory or supplementary endpoints.

2.4.4.3. Genotoxicity

Olezarsen was thoroughly evaluated for its genotoxic potential in both in vitro and in vivo studies. These studies were conducted to assess whether Olezarsen could induce genetic mutations, chromosomal damage, or other forms of genetic instability, which are key regulatory requirements for

pharmaceutical safety evaluation. All the studies were performed using olezarsen free acid, the form proposed for human use, and the impurity profile of the test material used was consistent with the batches used in clinical evaluations. Each assay followed Good Laboratory Practice (GLP) regulations and adhered to internationally recognized guidelines, specifically the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines (ICH S2(R1)) for genotoxicity testing and data interpretation.

Olezarsen's potential to cause gene mutations was first evaluated using the Ames bacterial reverse mutation test (Study ID 678354-IS01). In this assay, the compound was tested on various strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537) and the Escherichia coli strain WP2 uvrA, both with and without metabolic activation provided by the Aroclor 1254-induced rat liver S9 fraction. Concentrations of olezarsen ranged from 15 to 5000 µg/plate. The study's results demonstrated that olezarsen did not increase the number of revertant colonies in any of the bacterial strains at any concentration tested, with or without the S9 metabolic activation system. The absence of mutagenic effects was clear, and antibacterial toxicity was not observed up to the highest tested concentration. The study met all validity criteria, and positive controls produced the expected mutagenic responses, confirming that the assay was functioning as intended. Overall, this test concluded that olezarsen does not possess mutagenic potential in bacterial systems.

Next, olezarsen was evaluated for clastogenicity—its potential to cause chromosomal aberrations—using the chromosome aberration assay (Study ID 678354-IS02) in Chinese hamster lung (CHL) cells. This assay tested concentrations of 125, 250, and 500 µg/mL, with and without the addition of the Aroclor 1254-induced rat liver S9 fraction for metabolic activation. The study was designed to detect both structural and numerical chromosomal aberrations. Results showed that there was no significant increase in aberrant metaphases with structural or numerical chromosomal aberrations at any tested concentration of olezarsen, regardless of the presence of S9. The results fell within historical control data, and positive controls confirmed the validity of the assay. Consequently, olezarsen was considered negative for clastogenicity, meaning it did not cause chromosomal damage in CHL cells up to the highest concentration tested.

To complement the in vitro findings, olezarsen was tested for clastogenic potential in vivo using the mouse bone marrow micronucleus assay (Study ID 678354-AS05). This assay assessed whether olezarsen could induce micronuclei, which are indicative of chromosomal damage, in the bone marrow of male CD-1 mice. Olezarsen was administered subcutaneously at doses of 500, 1000, and 2000 mg/kg. Tissue exposure to olezarsen was confirmed by measuring liver concentrations, which ranged from 604 to 1407 µg/g. The study did not detect a statistically significant increase in the percentage of micronucleated polychromatic erythrocytes (MNPCE) in bone marrow samples at any of the doses tested when compared to the vehicle control. The results fell within historical control data, and no dose-response relationship was observed. As in the in vitro studies, the positive control (cyclophosphamide, CPA) confirmed the assay's validity, producing the expected significant increase in micronucleated cells. Therefore, olezarsen was concluded to lack clastogenic potential in vivo.

The use of rat liver S9 fraction in the in vitro assays is critical for evaluating whether metabolic activation might influence the genotoxicity of olezarsen, simulating the hepatic metabolism that occurs in humans. By testing both in the presence and absence of S9, the studies ensured that any potential genotoxic metabolites would be detected, but no mutagenic or clastogenic effects were found under either condition. The in vivo micronucleus assay in mice further supported these findings, as it is a well-established model for detecting chromosomal damage and clastogenicity and is widely accepted in regulatory genotoxicity testing due to its sensitivity and reliable response patterns

The genotoxicity evaluation of olezarsen, performed in vitro and in vivo, is comprehensive and follows ICH S2(R1) guidelines, providing a strong basis for assessing the safety profile of the compound. The studies were conducted in compliance with GLP standards, adding credibility to the findings.

In the in vitro Ames test (Study No. 678354-IS01), the mutagenic potential of olezarsen was assessed using Salmonella typhimurium strains (TA98, TA100, TA1535, TA1537) and Escherichia coli strain (WP2 uvrA). A broad range of concentrations, up to 5000 µg/plate, was tested, ensuring comprehensive coverage. Stability and concentration verification were performed, with no noted stability issues. The inclusion of a rat liver S9 fraction (Aroclor 1254-induced) for metabolic activation was relevant, simulating metabolic processes akin to those in human liver metabolism. The vehicle and positive controls, such as 2-AA and BP, showed appropriate responses, confirming the validity of the assay. No increase in revertant colonies was observed, indicating that olezarsen was not mutagenic. The absence of mutagenicity is well-supported by the data, with consistent results across strains and conditions.

In the in vitro chromosome aberration assay (Study No. 678354-IS02), olezarsen was evaluated for clastogenic potential using Chinese Hamster Lung (CHL) cells at concentrations of 125, 250, and 500 µg/mL. Both metabolic activation (+/- S9) conditions were included to ensure the assessment covered potential metabolic effects. The study used appropriate positive controls—cyclophosphamide monohydrate (CPA) and ethyl methanesulfonate (EMS)—which performed as expected, indicating assay validity. No cytotoxicity was observed at the highest concentration tested. The results showed no increase in chromosomal aberrations at any dose level, supporting a lack of clastogenic potential for olezarsen.

The in vivo micronucleus assay in male CD-1 mice (Study No. 678354-AS05) further assessed the clastogenic potential of olezarsen. The study was conducted using doses of 500, 1000, and 2000 mg/kg, selected based on a dose-finding study that established the maximum tolerated dose (MTD). Exposure to olezarsen was confirmed through liver tissue analysis, with concentrations ranging from 604 to 1407 µg/g, indicating adequate systemic exposure. Cyclophosphamide monohydrate at a dose of 40 mg/kg served as a positive control, which showed the expected increase in micronucleated polychromatic erythrocytes (MNPCE), thereby validating the assay. No statistically significant increase in MNPCE was observed at any dose of olezarsen compared to the negative control, indicating that olezarsen did not exhibit clastogenic effects in vivo.

The genotoxicity studies collectively demonstrate that olezarsen is neither mutagenic nor clastogenic under the tested conditions, supporting its safety profile for the proposed indication. The use of a rat liver S9 fraction is appropriate for assessing potential metabolic activation, and the in vivo study provided sufficient systemic exposure, relevant to human use. There is no evidence suggesting a genotoxic risk, and the margin of safety is adequate given the absence of positive findings in both in vitro and in vivo settings. Thus, olezarsen does not present a genotoxic hazard for human use under the tested conditions.

2.4.4.4. Carcinogenicity

Carcinogenicity studies were not conducted for olezarsen. Both the US FDA and EMA CHMP supported the decision not to conduct carcinogenicity studies with olezarsen based on the similarities in toxicity and pharmacokinetic (TK) profiles between volanesorsen and olezarsen (which is a GalNAc conjugated form of volanesorsen). These similarities were reviewed in detail by both agencies (IND 136692, FDA Advice Letter from 03/16/2021, and EMA CHMP Scientific Advice Letter on 06/25/2020). As a result, they determined that no additional carcinogenicity studies were required for olezarsen, and that the data from volanesorsen's carcinogenicity studies were sufficient to support olezarsen.

Volanesorsen, an unconjugated antisense oligonucleotide (ASO) of the same sequence as olezarsen, along with a mouse-specific apoC-III ASO (ISIS 440670), were evaluated for carcinogenic potential in standard 2-year studies in CD-1 mice and Sprague-Dawley rats (Study Nos. 304801-AS15 and 304801-AS16). These studies showed an increased incidence of neoplasms, but these findings were generally attributed to the high sensitivity of these species to the pro-inflammatory effects of oligonucleotides, rather than any inherent carcinogenic potential of volanesorsen.

Moreover, the toxicological findings, tissue distribution, exposure levels, and elimination kinetics of olezarsen are comparable to volanesorsen and other 2'-MOE ASOs, as demonstrated in pharmacokinetic (PK) studies. The pattern of metabolites observed in liver and kidney tissues was consistent with the expected oligonucleotide degradation, which involves initial endonuclease followed by exonuclease-mediated cleavage within the deoxy-gap portion of the molecule.

Furthermore, the safety margin of olezarsen, as determined from repeat-dose toxicity studies in mice, is 9- to 14-fold greater than the monthly clinical doses of 50 or 80 mg administered to humans. This safety margin was considered adequate to support its use without the need for additional carcinogenicity studies. The scientific rationale for this decision is further detailed in Section 9.9 of the document.

The applicant's justification for not conducting carcinogenicity studies for olezarsen aligns with the considerations of the ICH S1A guidelines. The key argument is that olezarsen and volanesorsen share similar toxicity and pharmacokinetic profiles. Volanesorsen has been thoroughly evaluated for carcinogenic potential in two-year rodent studies, supporting the position that additional carcinogenicity studies for olezarsen are not necessary. According to the guidelines, when a new compound is closely related to one with existing carcinogenicity data, especially in terms of metabolism and toxicity profile, repeating long-term studies may not provide new information. Additionally, both the FDA and EMA have supported the decision to forgo further carcinogenicity studies for olezarsen. This regulatory endorsement is significant because it considers the overall data package, including the similarity to existing compounds and the existing data from volanesorsen. The applicant also indicates that volanesorsen showed an increase in neoplasms in rodent studies; however, these findings were interpreted as species-specific responses to oligonucleotides rather than indicators of inherent carcinogenicity. The guidelines allow for the interpretation of such results, especially if the findings are not considered relevant to human risk. The applicant further supports their case by including mechanistic details, such as the metabolism of olezarsen through endonuclease and exonuclease activity and its tissue distribution, which are consistent with other similar compounds. The safety margins observed in repeat-dose toxicity studies of olezarsen are nine to fourteen-fold greater than the clinical doses, which suggests a low risk of unexpected carcinogenic effects in humans. The guidelines emphasize considering such safety margins when evaluating the need for carcinogenicity testing. Given the comprehensive evaluation of volanesorsen and the close similarities between olezarsen and volanesorsen, the applicant's justification for not conducting additional carcinogenicity studies is well-supported. The existing data, combined with regulatory acceptance, indicate that the carcinogenic risk of olezarsen is sufficiently characterized through the studies on volanesorsen, thereby meeting the criteria outlined in the ICH S1A guidelines.

2.4.4.5. Reproductive and developmental toxicity

The reproductive and developmental toxicity profile of olezarsen has been evaluated without the need for comprehensive embryo-foetal development or pre- and post-natal toxicity studies, as both the US FDA and EMA CHMP supported a waiver for these studies. This decision is based on the available data from volanesorsen, a compound that shares the same sequence and chemistry as the active moiety of olezarsen. Volanesorsen's reproductive toxicity studies in mice and rabbits demonstrated no significant

impact on foetal or maternal health, and its similar pharmacokinetic profile to olezarsen further supports the waiver for Segment II and Segment III studies.

A fertility assessment (Segment I) for olezarsen was conducted in mice, as recommended by both the FDA (IND 136692, End-of-Phase 2 Written Response, July 1, 2020) and EMA CHMP (Scientific Advice Letter, June 25, 2020), based on findings from a previous study with volanesorsen. In this prior study, decreased prostate/seminal vesicle weights and reduced sperm counts were observed. Study 678354-AS08 was subsequently designed to assess the effects of olezarsen on fertility, embryo development, and early stages of implantation in CD-1 mice.

In study 678354-AS08, male mice received subcutaneous (SC) doses bi-weekly for 10 weeks before mating and continued treatment for 14 weeks. Female mice received bi-weekly doses starting 2 weeks before mating and continued every other day until implantation (GD 6). The dose levels tested were 0, 5, 10, and 20 mg/kg. No treatment-related effects on fertility, embryonic development, or overall health parameters were observed in either males or females. Minor body weight changes were noted in males (up to 1.27-fold at 20 mg/kg), along with increases in liver, spleen, and kidney weights. However, these were not considered toxicologically significant. Slight increases in ALT levels and decreases in triglycerides were also noted at higher doses, but these changes did not impact reproductive outcomes. The study concluded that olezarsen was well-tolerated at doses up to 20 mg/kg, and the No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg.

Further analysis revealed no adverse effects on mating behaviour, fertility indices, or early embryonic development across all tested doses. Minor increases in liver, spleen, and kidney weights were observed, particularly at doses of 10 mg/kg and above, but these changes were considered adaptive and reversible, not indicative of long-term reproductive risks. The study adhered to ICH S5 (R3) guidelines for reproductive toxicity evaluation, utilizing a robust sample size of 22 males and 22 females per group, exceeding the recommended minimum. The study design, including four dose groups and subcutaneous administration, mirrored clinical administration practices, further supporting the relevance of the findings.

In addition to the fertility and early embryonic development (FEED) study, repeated-dose toxicity studies (13 and 26 weeks in CD-1 mice, and 13 and 39 weeks in cynomolgus monkeys) revealed no structural or functional changes in reproductive organs, including the testes and ovaries. This absence of reproductive organ toxicity further supports the reproductive safety profile of olezarsen at therapeutic doses.

The waiver for additional embryo-foetal development (Segment II) and prenatal and postnatal development (Segment III) studies for olezarsen is justified by the volanesorsen data. These studies showed no adverse effects on maternal health or offspring, and maternal and foetal exposure was minimal. EMA guidelines (ICH S5 (R3)) allow for such waivers when relevant safety data are available from a similar active substance, as is the case with volanesorsen. The volanesorsen data provide a strong basis for granting these waivers, as both the EMA and FDA have accepted the absence of reproductive toxicity.

Although no juvenile animal toxicity studies were conducted with olezarsen, data from volanesorsen's PPND study, which included foetal and infant exposure, showed no adverse effects on neonatal or infant development. Given that olezarsen and volanesorsen share the same sequence and chemical structure, the extrapolation of safety data from volanesorsen to olezarsen is scientifically justified. The absence of adverse effects in neonatal and infant development suggests that additional juvenile animal studies may not be necessary, provided the pharmacokinetic and exposure profiles remain consistent between the two compounds.

In conclusion, based on the available data from volanesorsen, no additional juvenile toxicity studies for olezarsen are warranted at this time. The existing safety profile, supported by volanesorsen studies, is sufficient to address concerns related to reproductive, prenatal, postnatal, and juvenile developmental toxicity for olezarsen.

2.4.4.6. Toxicokinetic data

The repeat-dose toxicity studies in CD-1 mice and cynomolgus monkeys provided toxicokinetic data, with parameters like AUC and Cmax being determined only in cynomolgus monkeys, showing dose-dependent increases in both tissue and plasma concentrations. In mice, safety margins were calculated based on AUC and Cmax data obtained from pharmacokinetic studies rather than from the toxicity studies themselves.

Mice

Following 13 weeks of treatment, ISIS 678354 was seen to be distributed to kidney and liver, with dose-dependent concentrations of unconjugated ISIS 678354 in both tissues that appeared to increase dose-proportionally in liver and greater than dose-proportionally in kidney. Almost complete clearance was seen after 13-week recovery.

Total full-length ASO was the most abundant species of oligonucleotide present in kidney and liver tissue, accounting for approximately 82% and 83% of the total oligonucleotides on Day 93. Shorter oligonucleotide metabolites of unconjugated ISIS 678354 were present with an average relative abundance for each metabolite < 7% of the total peak areas on Day 93. This pattern is consistent with initial endonuclease followed by exonuclease mediated cleavage of the oligonucleotide in the deoxy gap portion of the molecule.

Following subcutaneous administration for 26 weeks, ISIS 678354 distributed extensively to the kidney and liver in mice. Unconjugated ISIS 678354 concentrations were dose-dependent and increased as dose increased in a greater than dose-proportional manner (29-fold over a 10-fold dose range) in kidney and in a dose proportional manner in liver after s.c. administration in the dose range of 2 to 20 mg/kg/week. There was a trend for higher concentrations (3-fold) of unconjugated ISIS 678354 in the liver when compared to kidney at the 2 mg/kg/week dose only.

At the corresponding 20 mg/kg/week dose level and time point in liver and kidney tissues, ovary, testes and uterus concentrations were approximately 5- to 12- fold lower than the liver and kidney tissues.

Monkeys

Following 39 weeks of treatment, steady-state ISIS 678354 exposure in tissue was reached at or before 13 weeks of treatment in monkeys. Anti-ISIS 678354 antibodies were detected in 30% and 58.30 to 87.5% of monkeys receiving weekly SC injections of 30 and 2 to 12 mg/kg/week ISIS 678354, respectively, after 13 (30 mg/kg/week only) and 39 weeks of treatment.

With regards to immunogenicity developing olezarsen treated animals, even though plasma ISIS 678354 exposure in terms of Cmax or AUC0-48 was higher in IM positive animals compared to IM negative animals following 39 weeks of treatment, tissue exposure was similar between IM negative and IM positive animals. In addition, there were no apparent correlation between toxicology endpoints (C3, platelet and apoC-III mRNA level) and immunogenicity. The results led to the conclusion that immunogenicity had little to no effects on the PK parameters and toxicity findings.

FEED Study

Toxicokinetic data confirm dose-dependent increases of unconjugated olezarsen concentrations in the parental male and female liver and kidney

Interspecies comparison and exposure margins to clinical exposure

The interspecies comparison of olezarsen exposure between animals and humans, as outlined in the study, compares NOAELs, AUCs, C_{max} values, and calculated exposure margins.

In a 13-week study (Study 678354-AS02) conducted in cynomolgus monkeys, at a dose of 6 mg/kg/week, the NOAEL was set at 104 µg·h/ml for the animal AUC, with a C_{max} of 13.8 µg/ml. This dose yielded exposure margins relative to human data of 24.8/16.5 for males and 23.8/15.9 for females when considering the 66 mg/50 mg human doses.

For the 39-week study in cynomolgus monkeys (Study 678354-AS02), also at 6 mg/kg/week, the NOAEL was 116 µg·h/ml with a C_{max} of 16.7 µg/ml. The exposure margins at this dose were 39.5/26.3 for males and 27.6/18.4 for females, based on the comparison to human doses of 105.4 mg and 57.3 mg.

In mice (Study 678354-AS04), CD-1 mice received a 6 mg/kg/week dose, with a reported animal AUC of 14.3 µg·h/ml. In another instance, CD-1 mice on a cumulative dose of 24 mg/kg showed an AUC of 57.4 µg·h/ml and a C_{max} of 13.79 µg/ml, with exposure margins of 13.79/1.1.

In study 678354-AS05 (CD-1 mice), at 20 mg/kg/week, the animal AUC was 47.8 µg·h/ml, with no reported C_{max} values. Exposure margins for this dose were calculated at 11.4/15.17 based on human equivalents.

Estimated cumulative $AUC_{0\text{-}48h}$ for 6 mg/kg/week (24 mg/kg/month) in mice based on actual $AUC_{0\text{-}48h}$ from weekly dosing of 10 mg/kg ($AUC_{0\text{-}48h}$ = 23.9 µg*hr/mL) from the Study No. 678354-APK01.

For humans, the estimated plasma AUC at a steady state for a 50 mg/month dose was reported as 63.3 µg·h/ml based on the PK model developed from the ISIS 678354-CS1 and CS2 studies. For the 105 mg/month human dose, the human AUC was estimated to be 158.4 µg·h/ml, and for the 40 mg/month dose, the human AUC was estimated at 40.9 µg·h/ml. This comparison outlines the relationship between the animal and human exposures to guide safety margins for clinical exposure of olezarsen.

Based on the ICH guidelines, particularly ICH S3A and M3(R2), toxicokinetic (TK) data are required to assess systemic exposure during toxicity studies. The primary objective of toxicokinetics is to describe systemic exposure in animals and its relationship to dose levels, as well as the time course of the toxicity studies. Typically, plasma, whole blood, or serum concentrations are used to measure exposure parameters such as AUC (Area Under the Curve) and C_{max}, which help to interpret the toxicological findings and their relevance to clinical safety.

The guidelines emphasize that toxicokinetic measurements should be integrated into toxicity studies, rather than conducted as separate pharmacokinetic studies, unless specifically justified. This integration is critical because it links the toxicological effects observed in toxicity studies with systemic exposure. In studies related to reproductive toxicity, genotoxicity, or carcinogenicity, toxicokinetic data provide essential information for comparing exposure levels across species. However, in some cases, tissue exposure data may also be sufficient, depending on the study design and context.

In the case of olezarsen, toxicokinetic plasma data were collected only in studies with Cynomolgus monkeys (e.g., study 678354-AS02). In other repeated-dose toxicity studies conducted with CD-1 mice, tissue exposure data were used instead of plasma measurements. According to the ICH guidelines, it is acceptable to calculate safety margins based on pharmacokinetic data from these

studies, provided that the exposure measurements accurately reflect the systemic exposure on the test species under the specific toxicity study conditions.

The safety margins derived from these data indicate that the exposure levels in animals are significantly higher than those anticipated for human clinical exposure. Specifically, for Cynomolgus monkeys, the safety margins are favourable, particularly at higher (cumulative) doses, which suggests that the exposure in monkeys provides a robust margin of safety. Although the safety margins for CD-1 mice are lower compared to Cynomolgus monkeys, they remain within acceptable limits for drug safety assessments. According to ICH M3(R2) guidelines, the recommended safety margin typically ranges from 10- to 50-fold. In this case, the cumulative dose of 24 mg/kg/month in monkeys exceeds a 50-fold margin, with safety margins ranging from 66 to 158 in males and 63.5 to 110.5 in females. This is particularly important if, following clinical evaluation, there is a proposal to increase the therapeutic dose in humans due to an insufficient pharmacodynamic effect of olezarsen.

2.4.4.7. Local Tolerance

Studies specifically designed to evaluate the local tolerance of olezarsen were not conducted. Instead, the SC injection sites were evaluated as part of the repeat-dose studies in mice and monkeys. Aside from the expected proinflammatory effects in rodents, there was no evidence of substantive irritation.

The applicant’s approach to assessing the local tolerance of olezarsen by evaluating SC injection sites within the context of repeat-dose toxicity studies in mice and monkeys, rather than conducting separate local tolerance studies, aligns with the principles outlined in the EMA guideline EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1. This approach is acceptable, particularly given that local tolerance evaluation can be integrated into repeat-dose studies, as recommended by the guideline, to reduce the need for additional animal test.

However, it is important to note that the guideline emphasizes the need to specifically address local tolerance at the intended clinical contact sites, distinguishing local toxicological effects from physical consequences such as trauma. The applicant's statement that "there was no evidence of substantive irritation aside from expected proinflammatory effects in rodents" suggests that no significant adverse effects were observed at the injection sites, but still, it is not entirely clear if the effects are test related or simply due to the injection itself. Other toxicity studies

Antigenicity

The non-clinical summary document of study 678354-AS02 includes immunogenicity assessments for anti-olezarsen antibodies in plasma samples taken at various time points (pre-dose on Days 1, 91, 182, 273, and 455) during and following 13 or 39 weeks of treatment. Anti-olezarsen antibodies were found in 27.7% of animals receiving weekly subcutaneous injections of 30 mg/kg/week and ranged from 25.0% to 62.5% in animals treated with 2 to 12 mg/kg/week olezarsen. Immunogenicity-positive animals were detected at all assessed time points, with the highest incidence generally observed on Day 182. Despite the presence of anti-olezarsen antibodies, there were no significant differences in olezarsen exposure parameters (C_{max}, $AUC_{0\text{-}48h}$) or efficacy, as measured by the inhibition of apoC-III mRNA and protein expression, between immunogenicity-negative and immunogenicity-positive animals after up to 39 weeks of treatment.

The study provides robust data on the pharmacokinetics and toxicokinetics of ISIS 678354, including total full-length antisense oligonucleotides (ASO) and unconjugated ISIS 678354 in plasma and tissues. However, regarding immunogenicity, the incidence of anti-drug antibodies (ADA) was notable, with 25.0% to 62.5% of monkeys developing antibodies after 9 months of treatment at doses between 2 to 30 mg/kg. This level of immunogenic response could potentially influence the pharmacokinetics of

ISIS 678354, however the data does suggest that the immunogenic response in these animals did not dramatically influence the pharmacokinetics of ISIS 678354, particularly in terms of C_{max} and terminal half-life. The observed increase in AUC on Day 273 may indicate some effect, but it's not strong enough to conclude a broad impact on the overall pharmacokinetic profile.

While tissue exposure did not show a clear distinction between immunogenic-positive and immunogenic-negative animals, and despite the observed increase in AUC on Day 273 in immunogenic-positive animals, there is no strong evidence to suggest that the presence of anti-drug antibodies significantly alters the pharmacokinetics of ISIS 678354. The similar tissue concentrations across groups indicate that antibody formation does not appear to affect tissue distribution or clearance in a meaningful way.

Immunogenicity

In a 9-month chronic toxicology study in monkeys, immunotoxicity was evaluated with particular focus on the production of plasma complement split product Bb. Olezarsen treatment resulted in acute, transient, and dose-dependent elevations in Bb levels. At doses of 12 mg/kg/week and 30 mg/kg/week, Bb levels increased by approximately 3-fold in females and up to 21-fold in both males and females, relative to pre-study values on Day 1. These elevations peaked at 4 hours post-dose and generally returned to baseline within 24 hours. Similar patterns of Bb elevation were observed on Days 91, 182, and 273, with increases up to approximately 3.6-fold in males and 5.5-fold in females at doses of ≥2 mg/kg/week. The increases in Bb were accompanied by minimal to slight reductions in total C3 levels, although these reductions were dose-independent, both at pre-dose and 24 hours post-dose, after 13 or 39 weeks of treatment compared to baseline values.

Dose-dependent effects on complement factors were observed, particularly with a decrease in C3 and an increase in Bb concentrations. This suggests some degree of complement activation, but these effects were reversible during the recovery period. Complement activation can be an indicator of potential immunotoxicity, but in this study, the changes were transient and reversible.

Studies on metabolites

The pattern of metabolites observed in the liver and kidney is consistent with initial endonuclease-mediated cleavage, followed by exonuclease-mediated cleavage of the oligonucleotide in the deoxy-gap portion of the molecule. Toxicokinetic studies show that the majority of olezarsen remains in its full-length, conjugated form, with shortmer metabolites present at lower levels. These shortmer metabolites were detected at low concentrations across both mouse and monkey studies. The concentrations observed in the repeat-dose toxicity studies suggest that they are unlikely to accumulate to levels associated with toxicity. Based on this metabolic profile and the absence of adverse findings related to metabolite accumulation, the available data are sufficient to conclude that the identified metabolites do not pose a significant toxicological risk. Therefore, no additional studies on metabolites are necessary currently.

Studies on impurities

In the 13-week Repeat Dose Toxicity and Impurity Qualification Study of Olezarsen and Associated TAMs in CD-1 Mice (Study No. 678354-AS06), the toxicity of olezarsen and its associated impurities (TAM #1, TAM #2) was evaluated. Ten animals per sex per group were administered weekly subcutaneous (SC) doses of saline, olezarsen, or TAMs at dose levels of 2.33 or 7 mg/kg/week. The tested impurities included dithioate (~5.1%) and MOE amidite impurities (e.g., 2′-O-Methyl/loss of acetyl and 3′-O-Methyl).

Significant toxicological findings were observed in the liver, spleen, and injection site. Liver toxicity included mononuclear cell infiltration, extramedullary haematopoiesis, single-cell necrosis, nuclear

degeneration, cytomegaly/karyomegaly, and increased mitosis at both dose levels. These liver effects were associated with elevated ALT and AST levels and increased liver weights. While both olezarsen and TAM-treated groups exhibited similar microscopic liver changes, the severity of liver necrosis was slightly higher in TAM-treated animals.

Other findings included reductions in glucose and alkaline phosphatase (ALP) and increases in inorganic phosphorus (IP) levels. Overall, the study concluded that olezarsen and its impurities produced a similar toxicological profile, with no significant exacerbation of toxicity by the impurities at the tested levels.

The data provided on the qualification of impurities, including the 13-week repeat-dose toxicity study in CD-1 mice (Study No. 678354-AS06), addresses the evaluation of olezarsen and its associated impurities. The study includes an assessment of test article mixtures (TAMs) with olezarsen and elevated levels of specific impurities such as dithioate and MOE amidite impurities.

In the liver, microscopic findings such as single-cell necrosis, nuclear degeneration, cytomegaly/karyomegaly, and increased mitosis were observed across all treatment groups, including those exposed to olezarsen alone and to the TAMs (TAM #1 and TAM #2). While these findings were evident in both sexes, their incidence and severity were slightly higher in the TAM-treated groups, particularly for single-cell necrosis in males and females at 7 mg/kg/week. These liver findings were correlated with increased liver enzyme levels (ALT, AST) and liver weight increases. Such effects may be indicative of a pro-inflammatory response due to oligonucleotide accumulation.

Although the impurities appeared to exacerbate liver effects slightly, the overall toxicological profile between olezarsen alone and the TAMs was not markedly different. This suggests that while impurities contribute to the toxicological burden, they do not significantly alter the safety profile when compared to olezarsen alone.

The impurities level in the final drug was not mentioned in the non-clinical summary, but it was further clarified in the non-clinical overview. The qualification of these impurities at the levels tested (up to 7 mg/kg/week) appears to be within acceptable safety margins for the proposed clinical use of olezarsen. However, the final determination would depend on confirming this consistency in the quality module.

Phototoxicity

For drugs administered subcutaneously, phototoxicity studies are usually not required. No data have been provided indicating that ISIS 678354 binds to melanin or keratin, which would suggest tissue (skin) retention and/or accumulation could occur.

2.4.5. Ecotoxicity/environmental risk assessment (ERA)

The following justification was submitted by the applicant for the lack of ERA:

"Olezarsen is a -O-2- -MOE)-modified chimeric gapmer antisense oligonucleotide (ASO) conjugated to triantenary N-acetyl galactosamine (GalNAc) with a backbone of phosphorothioate internucleotide linkages. ASOs are short synthetic strings of nucleotides that, in the case of olezarsen, are designed to prevent expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein, thereby preventing translation. In natural environmental matrices (e.g, surface water, soil, sediment), olezarsen is considered to be non-hazardous due to its potential for rapid degradation by abiotic and biotic mechanisms. The environmental risk is considered to be negligible and, in accordance with EMA guideline (CHMP 2024), ERA studies are not submitted. Although olezarsen is not a naturally occurring product and the conjugated GalNAc is synthetic material, the major constituents are natural components (i.e., nucleotides, amino sugars) and are

expected to rapidly metabolize within the body and not be excreted. As such olezarsen is not expected to enter into wastewater and subsequently the environment as an intact medicinal substance. Therefore, this assessment concludes there are no perceivable risks to the environment. Additional discussion on the degradation potential of olezarsen was also provided. In conclusion and in accordance with the EMA guideline (CHMP 2024), studies to assess the environmental fate and effects of olezarsen are not required to be submitted. Furthermore, no special precautions are required to mitigate the release of the medicinal product to the environment that will result from its use in patients or disposal of the product. Therefore, it is not considered necessary to include warnings or precautions within the product information in relation to environmental risks.

2.4.6. Discussion on non-clinical aspects

Pharmacology. The MoA of olezarsen was confirmed (in *in vitro* PD studies) showing that it selectively targets human apoC-III mRNA resulting in significant (82%) activity reduction. Potential off-target sites (e.g., in oesophagus, lung, spleen, uterus etc.) were identified and the potency of the test article for them needs to be clarified and raised as OC. In *in vivo* PD studies using human apoC-III transgenic mice, olezarsen demonstrated a ~13-fold potency improvement in reducing apoC-III and plasma TG in comparison to volanesorsen. Olezarsen also demonstrated firm activity in non-human primates, with > 80% reductions in liver and plasma apoC-III reduction at doses of 6 mg/kg.

Secondary PD studies. Omission of dedicated secondary pharmacodynamics studies in animals is acceptable as olezarsen specifically targets human apoC-III mRNA and secondary off-target actions are expected to be minimal.

Safety pharmacology. Studies carried out in monkeys have not revealed effects on safety pharmacology parameters including CNS, heart and respiratory, and no blocking of hERG current. In addition, Safety pharmacology issues in relation with toxicology findings are comprehensively addressed by the applicant, who discussed potential toxicity related to apoC-III reduction, observations associated with plasma kinetics, tissue distribution and cellular uptake, effects on liver, kidney, on thrombocytopenia and haematology, on complement activation, effects of anti-olezarsen antibody.

Pharmacodynamic drug interactions. Dedicated studies were not performed. The olezarsen was evaluated in *in vitro* studies to assess the potential for involvement in CYP-, transporter-, or plasma protein binding-mediated drug-drug interactions.

Pharmacokinetics. The pharmacokinetic profile of olezarsen has been characterized using mice and monkeys. Monkey is considered the most relevant species to humans based on the general pharmacokinetic behaviour of olezarsen (T_{max}, plasma AUC, $t_{1/2}$, and clearance). Majority of studies were conducted in line with GLP requirements and bridged from toxicology investigations, therefore, dosing exceeded clinically relevant exposures.

Absorption. The data submitted fulfil the requirements and evidenced that after repeated dosing of olezarsen, mean peak and total plasma exposure (C_{max} and $AUC_{0\text{-}48h}$) values were like those following the first dose, suggesting that plasma PK was unaltered after repeated dosing and that there was no accumulation in either C_{max} or $AUC_{0\text{-}48h}$ with repeated dosing for up to 39 weeks in monkeys. In summary, the applicant's conclusions based on non-clinical studies and literature overview that distribution of olezarsen to liver is attributed to the more efficient ASGPR-mediated uptake in hepatocytes for GalNAc conjugated ASOs at clinically relevant doses is considered relevant. Consequently, the ability to achieve similar pharmacologic response with a lower dose with the $GalNAc_3$-conjugated ASO enables reduction in dosing (80 mg compared to 285 mg of volanesorsen) and change the frequency from weekly to monthly.

Distribution. The initial rapid plasma clearance in both mice and monkeys is attributed to extensive distribution of olezarsen to tissues, resulting in the highest concentrations in the liver, the target organ for pharmacology, and the kidney. The dose dependent hepatocyte uptake in monkeys is expected to be translatable to humans. In relation to findings in the dedicated olezarsen and volanesorsen distribution studies and observed predominance of olezarsen uptake in kidney and other organs that are not target organs, possible safety issues could arise, particularly with dose increase relation with prolonged persistence and signals from toxicology studies), particularly after long term administration of the test article in humans.

Metabolism. Studies revealed that olezarsen biotransformation of olezarsen is related to the endo- and exo- nuclease-mediated hydrolysis to form chain-shortened metabolites. 11 metabolites were detected. Clarification for not performing urine sample testing in monkeys was provided by the applicant. Urinary collection was indeed prohibited by the animal welfare regulation from Environment and Consumer Protection (LANUV) at the in-life animal facility. Therefore, literature data were given on both urinary excretion and metabolite profiles of this class of compound, being similar across monkey, rat and human. Minimal renal excretion and metabolites of (GalNAc)-conjugated ASOs were also described for monkeys, which are known to be consistent with those observed in humans.

Excretion. This PK parameter was evaluated in study with CD1 male mice only. No excretion in feces assays with olezarsen were conducted. Thus, excretion investigations with olezarsen in non-clinical package are considered scant. In respect of the 3R principle and investigations in humans, no new excretion studies in animals are warranted.

PK DDI. The DDI issues are considered addressed correctly and relevant information is presented in SPC section 4.5.

Toxicology. The results of olezarsen toxicology studies indicated that the drug was generally well tolerated across various dose levels in both CD-1 mice and cynomolgus monkeys. The studies included evaluations of repeated-dose toxicity, genotoxicity, reproductive toxicity. Single-dose toxicity studies were not conducted as standalone studies, following the ICH M3 (R2) guidelines. Acute toxicity information was obtained through dose-escalation studies and other analyses, such as the micronucleus test. However, this approach may not fully replace traditional single-dose toxicity studies, although the acute toxicity obtained from the repeat dose toxicity study in monkey is accepted.

Sub-chronic and chronic toxicity studies were conducted in both mice and monkeys, with doses ranging from 2 to 30 mg/kg/week in monkeys and 2 to 24 mg/kg/week in mice. Key findings included dose-dependent organ weight changes, increases in liver enzymes, and haematological alterations. Most effects, such as liver hypertrophy and macrophage infiltration, were reversible following a recovery period. The No Observed Adverse Effect Level (NOAEL) was established at 6 mg/kg/week in monkeys and 24 mg/kg/week in mice in a 13-week study. However, in a 26-week study, the NOAEL for mice was reduced to 6 mg/kg/week.

Olezarsen did not show genotoxic potential in vitro or in vivo. The Ames test, chromosome aberration assay, and micronucleus assay all returned negative results for mutagenicity and clastogenicity. In a reproductive toxicity study in mice, there were no treatment-related effects on fertility, embryonic development, or reproductive health at doses up to 20 mg/kg. No additional embryo-foetal development studies were conducted, with data from a related compound, volanesorsen. There was some evidence of immunotoxicity, such as dose-dependent increases in complement split product Bb in monkeys, though these effects were acute, transient, and reversible, without significant changes in immunoglobulin levels. Plasma toxicokinetic data were primarily available from monkey studies, while tissue distribution studies were performed in mice, showing dose-dependent accumulation in organs such as the liver and kidneys. However, the lack of plasma toxicokinetic data in the mouse studies poses a limitation. Several analyses in the repeated-dose toxicity studies, such as cytokine and

immunoglobulin evaluations, were conducted under non-GLP conditions. Carcinogenicity studies were not conducted for olezarsen, which was accepted based on similarities with volanesorsen, a related compound that underwent carcinogenicity testing. These studies predict that potential adverse events in humans could include liver toxicity, haematological changes, and complement activation. The effects were generally dose-dependent and reversible, suggesting that the drug's adverse effects may be manageable at therapeutic dose levels. In general, the rationale for the selection of species, study duration, and doses or concentrations used in toxicology studies is based on the need to reflect human exposure and potential toxicity as closely as possible, following regulatory guidelines such as ICH M3 (R2). The species chosen are typically from both rodent and non-rodent categories, as this provides a broad comparative understanding of how the drug may behave across different biological systems. For olezarsen, CD-1 mice (rodent species) and cynomolgus monkeys (non-rodent species) were selected. Mice are a common model due to their well-characterized physiology, genetic tractability, and historical use in drug testing, while cynomolgus monkeys were chosen because their metabolic and physiological systems are more closely aligned with humans, particularly in pharmacokinetics and immunological responses. Non-rodents, such as monkeys, are often required in studies to meet regulatory demands for data on species that more closely represent human drug metabolism and toxicity.

The duration of the studies is aligned with the anticipated human exposure. Sub-chronic (13-week) and chronic (26- or 39-week) toxicity studies were used to model both medium- and long-term exposure scenarios. These timeframes allow researchers to assess cumulative toxicity, recovery potential, and long-term effects that may arise from sustained drug use, which is important in predicting potential human responses to chronic therapy. The use of recovery phases in these studies also provides insight into whether any toxic effects are reversible once the drug is withdrawn.

The dose levels chosen for the studies typically include a range of doses, starting from low doses (at or near the anticipated therapeutic range) and escalating to higher doses to identify the no observed adverse effect level (NOAEL) and the maximum tolerated dose (MTD). For olezarsen, doses in mice ranged from 2 to 24 mg/kg/week, while in monkeys, they ranged from 2 to 30 mg/kg/week. These doses are designed to evaluate dose-dependency in toxicity, identify safety margins, and support dosing strategies for human clinical trials. According to ICH M3(R2) guidelines, the recommended safety margin typically ranges from 10- to 50-fold. In this case, the cumulative dose of 24 mg/kg/month in monkeys exceeds a 50-fold margin, with safety margins ranging from 66 to 158 in males and 63.5 to 110.5 in females. This is particularly important if, following clinical evaluation, there is a proposal to increase the therapeutic dose in humans due to an insufficient pharmacodynamic effect of olezarsen.

For olezarsen, the observed effects in both mice and cynomolgus monkeys included dose-dependent organ weight changes (e.g., increased liver and spleen weights), alterations in haematological parameters (e.g., reduced red cell mass, elevated neutrophils), and reversible increases in liver enzymes (ALT and AST). The applicant suggests that these effects, while observable in preclinical models, are manageable and may not pose significant risk to humans at therapeutic doses, particularly since the effects were mostly reversible during recovery periods. The claim that the reversibility of these findings suggests a manageable toxicity profile for chronic human use seems reasonable given the data, especially considering the No Observed Adverse Effect Level (NOAEL) established at 6 mg/kg/week in monkeys and 24 mg/kg/week in mice.

The applicant highlights the tissue accumulation of olezarsen, particularly in the liver and kidneys, as dose-dependent and reversible, asserting that these findings do not pose a significant risk for long-term human use. This is an area where human relevance can be concluded with moderate confidence. While tissue accumulation is not inherently problematic, the persistence of the drug in tissues and its slow clearance raise concerns about the potential for cumulative toxicity, especially in cases of prolonged treatment. The applicant’s reliance on animal recovery data to suggest that these effects will

not carry over into humans needs careful interpretation, particularly when considering species differences in metabolism and drug clearance.

Regarding impurities, the impurity profile of olezarsen in non-clinical studies should reflect that of the final product. The impurity qualification studies revealed liver-related toxicological findings linked to specific impurities (e.g., dithioate and MOE amidite impurities). Therefore, any variation in impurity levels between the non-clinical material and the marketed product could affect the safety profile, requiring additional evaluation to ensure consistency in toxicity risk assessment.

In the case of olezarsen, interspecies comparisons of metabolism and systemic exposure are essential for translating animal study findings to human safety. The non-clinical studies in CD-1 mice and cynomolgus monkeys provided toxicokinetic data, including parameters like AUC (area under the curve) and C_{max} (maximum concentration), which showed dose-dependent increases in tissue and plasma concentrations.

Cynomolgus monkeys, due to their closer metabolic and physiological similarity to humans, provide a more reliable model than mice for predicting human outcomes. However, the tissue retention of olezarsen observed in monkeys, particularly in the liver and kidneys, highlights the potential for cumulative toxicity, which may be relevant for humans, especially with long-term use. While the non-clinical studies offer valuable insights into potential adverse effects in humans, such as liver and kidney the differences in metabolism and systemic exposure between species emphasize the need for cautious interpretation. These studies provide a basis for predicting human outcomes, but certain adverse effects may not be fully extrapolated from animal models.

For genotoxicity, the studies conducted did not show any mutagenic or clastogenic potential, with negative results in the Ames test, chromosome aberration assay, and in vivo micronucleus assay. Therefore, the relevance of genotoxicity to humans appears to be low. Carcinogenicity studies were not conducted, as the applicant relied on data from a related compound, volanesorsen, which showed no significant carcinogenic effects. This rationale was accepted by both regulatory authorities (US FDA and EMA CHMP) and is considered applicable to humans, though the absence of direct carcinogenicity data for olezarsen itself does leave some uncertainty. In terms of reproductive and developmental toxicity, no adverse effects were observed in fertility and early embryonic development studies in mice, and additional developmental toxicity studies were waived based on volanesorsen data. The applicant suggests that these findings indicate a low risk of reproductive toxicity for humans. However, it is important to carefully assess whether the data from volanesorsen can be fully extrapolated to olezarsen, especially given the differences in study designs and potential pharmacokinetic differences. Overall, the findings in these areas suggest a manageable risk profile for human use, but the lack of direct carcinogenicity and full reproductive toxicity data for olezarsen introduces some limitations to the conclusions.

Section 4.3 (Contraindications) of the SmPC aligns with the submitted data, as hypersensitivity reactions were observed during clinical trials, justifying its inclusion. Although non-clinical studies did not demonstrate significant clinical hypersensitivity reactions, findings related to immune responses—such as complement activation indicated by a decrease in C3 and an increase in Bb—suggest a potential role in hypersensitivity reactions. However, these immune responses did not manifest as overt hypersensitivity in animal models. Therefore, the contraindication for hypersensitivity is appropriately based on clinical findings, with complement activation as a possible mechanistic contributor. Section 4.6 (Pregnancy and Lactation) of the SmPC is consistent with the non-clinical data. The animal studies showed no adverse effects on fertility, embryofoetal development, or post-natal development, supporting the low predicted risk during pregnancy. While no direct studies on lactation were conducted with olezarsen, the related compound volanesorsen demonstrated low excretion in milk and poor oral bioavailability, justifying the cautious wording in this section. Section 5.3 of the

SmPC accurately reflects the non-clinical data, confirming no special hazards for humans. Genotoxicity studies showed no relevant risks, and carcinogenicity data, derived from volanesorsen, indicated that the observed neoplasms were related to species-specific responses rather than an inherent carcinogenic potential. Reproductive and developmental toxicity studies indicated no adverse effects on fertility or embryofoetal development. Immunogenicity was noted with anti-drug antibodies in monkeys but did not significantly alter pharmacokinetics. Repeated-dose toxicity studies showed reversible mild haematological changes, supporting the overall safety profile of olezarsen.

ERA:

The applicant provided sufficient justification that the GalNAc–THA linker portion is rapidly metabolised into non-hazardous, low-molecular-weight, water-soluble compounds. Although the GalNAc–linker is not an active substance, it is chemically defined and may be considered environmentally relevant due to its potential release as part of excreted metabolites. According to the updated guidelines (EMEA/CHMP/SWP/4447/00 Rev. 1) and the associated Phase I decision tree, the substance does not qualify for exemption under Q1 (not a naturally occurring substance) or Q2a (not an Article 10 application). Furthermore, the GalNAc–THA conjugate is not a non-natural peptide or protein, rendering Q3a and Q3b not applicable. Consequently, the ERA assessment proceeds through Q4–Q7.

Although no formal PECsw calculation was submitted to verify whether the action limit of 0.01 µg/L is exceeded, the applicant has provided sufficient metabolic and structural data to conclude that environmental exposure is likely to be very low. The GalNAc–THA moiety is extensively metabolised in vivo across species, with rapid elimination and no indication of persistence or bioaccumulation. The degradation products are structurally simple, highly water-soluble, and lack reactive or environmentally hazardous functional groups. Additionally, the low and infrequent dosing (monthly subcutaneous administration) and the absence of direct release into wastewater pathways further support a negligible environmental burden.

Taken together, the available data on the metabolic fate, chemical structure, and dosing characteristics of the GalNAc–THA linker provide a reasonable scientific basis to conclude that the predicted environmental concentration in surface water (PECsw) is unlikely to exceed the action limit of 0.01 µg/L. The substance does not exhibit a specific toxicity profile, and the degradation products are expected to be structurally simple, highly water-soluble, and non-hazardous. Furthermore, the substance is administered subcutaneously at low and infrequent doses, with no indication of direct release into wastewater streams or potential for environmental persistence or bioaccumulation. In light of these considerations, exemption from further environmental risk assessment under Q7 of the decision tree in EMEA/CHMP/SWP/4447/00 Rev. 1 is considered scientifically justified.

Considering the above data, olezarsen is not expected to pose a risk to the environment. The concern regarding the GalNAc moiety is considered resolved.

2.4.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for olezarsen, were considered adequate and acceptable for the assessment of non-clinical aspects.

2.5. Clinical aspects

2.5.1. Introduction

Bioanalytical methods for quantification of drug (i.e., olezarsen and total full antisense oligonucleotides (ASOs)), biomarkers for pharmacodynamic/efficacy assessment including apoC-III, TG, apolipoprotein B (apoB)-48, non-high-density lipoprotein cholesterol (non-HDL-C), total apoB, very-low-density lipoprotein cholesterol (VLDL-C), chylomicron-TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A (apoA)-1, lipoprotein (a) [Lp(a)], remnant cholesterol concentrations, and detection of anti-drug antibodies (ADAs) were developed and properly validated.

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Number (Status)	**Study Design**	**Study Population**	**Objectives**	**Dosing Regimen, Route, and Duration of Administration**	**Number of Patients Evaluable for PK**
ISIS 678354 CS1 (completed)	A placebo-controlled, dose-escalation single and multiple-dose study	Healthy volunteers	Safety, Tolerability, PD, PK	Single-Dose Single SC doses of 10, 30, 60, 90, or 120 mg olezarsen, or placebo Multiple-Dose Q1W SC doses of 15 or 30 mg olezarsen for 6 weeks, or Q4W SC doses of 60 mg olezarsen for 13 weeks, or placebo	67, conventional PK parameters unless stated otherwise
AKCEA-CS1 (completed)	A randomized, placebo-controlled, double-blind, SAD and multiple-dose study	Healthy Japanese male and female participants conducted in the USA	Safety, Tolerability, PD, PK	Single-Dose Single SC doses of 30, 60, or 90 mg olezarsen, or placebo Multiple-Dose Q4W SC doses of 60 mg olezarsen or placebo up to 12 weeks	22, conventional PK parameters unless stated otherwise

ISIS 678354-CS20 (completed)	Phase 1, single dose, randomized, open-label 2-period crossover study	Healthy adult volunteers	Safety, BE of SC olezarsen at 2 dose levels and 2 different drug product presentations (autoinjector and vial), PD	Periods 1 and 2 Single SC doses of 50 mg or 80 mg olezarsen, with a 28- to 42-day washout between study periods	104, conventional PK parameters unless stated otherwise
Study Number (Status)	**Study Design**	**Study Population**	**Objectives**	**Dosing Regimen, Route, and Duration of Administration**	**Number of Patients Evaluable for PK**
ISIS 678354-CS2 (completed)	A randomized, double-blind, placebo-controlled, dose-ranging study	Patients with HTG and established CVD or at High Risk for CVD	Safety, Tolerability, Efficacy, PD, PK	Q4W SC doses of 10 mg olezarsen, Q4W SC doses of 50 mg olezarsen, Q2W SC doses of 15 mg olezarsen, or Q1W SC doses of 10 mg olezarsen, or placebo, for 52 weeks	89, conventional PK parameters unless stated otherwise
ISIS 678354-CS3 (completed)	Phase 3, randomized, double-blind, placebo-controlled, pivotal study	Patients with FCS	Efficacy, Safety, PK	Q4W SC doses of 50 mg or 80 mg olezarsen, or placebo, for 13 doses	43, conventional PK parameters unless stated otherwise
ISIS 678354-CS8 (completed)	Phase 2b randomized, double-blind, placebo-controlled study	Patients with HTG and athero-sclerotic CVD and/or with severe HTG	Safety, Tolerability, PK	Q4W SC doses of 50 mg or 80 mg olezarsen, or placebo, for 13 doses	115, conventional PK parameters unless stated otherwise
ISIS 678354-CS7 (ongoing)	Phase 3 open-label safety study	Patients with FCS transitioning from volanesorsen to olezarsen	Safety, Tolerability, PD, PK	Q4W SC doses of 80 mg olezarsen, or placebo, for up to 3 years	24, conventional PK parameters unless stated otherwise
ISIS 678354-CS13 (ongoing)	Phase 3 open-label extension study	Patients with FCS	Safety, PK	Q4W SC doses of 50 mg or 80 mg olezarsen, or placebo, for up to 3 years	54, conventional PK parameters unless stated otherwise

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

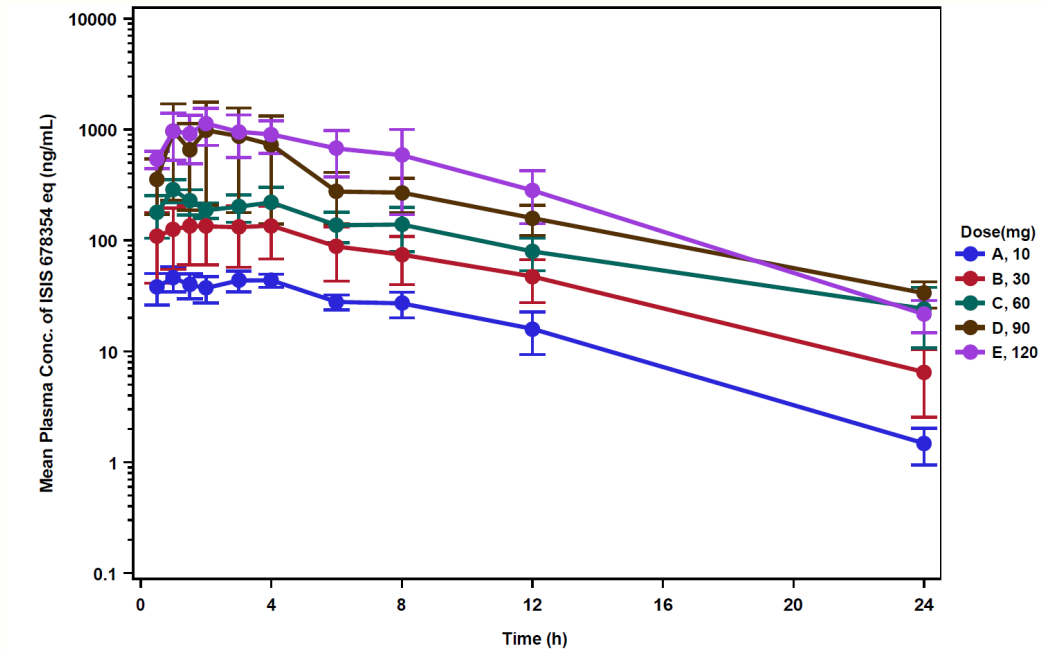
The summary of PK, PD, PK/PD, E-R relationship, and/or immunogenicity of olezarsen, QT/QTc prolongation potential is based on 3 completed Phase 1 clinical studies conducted in healthy volunteers (Studies ISIS 678354-CS1, AKCEA-CS1, and ISIS 678354-CS20), 2 Phase 2 studies in patients with hypertriglyceridemia (ISIS 678354 CS2 and ISIS 678354-CS8), a Phase 3, randomized, double-blind, placebo controlled study in patients with FCS (ISIS 678354-CS3), and two ongoing open-label safety studies (ISIS 678354 CS13 and ISIS 678354-CS7).

Absorption

The pharmacokinetic (PK) properties of olezarsen were evaluated following subcutaneous administration of single and multiple doses (once every week, and once every 4 weeks) in healthy subjects and multiple doses (once every 4 weeks) in patients with FCS.

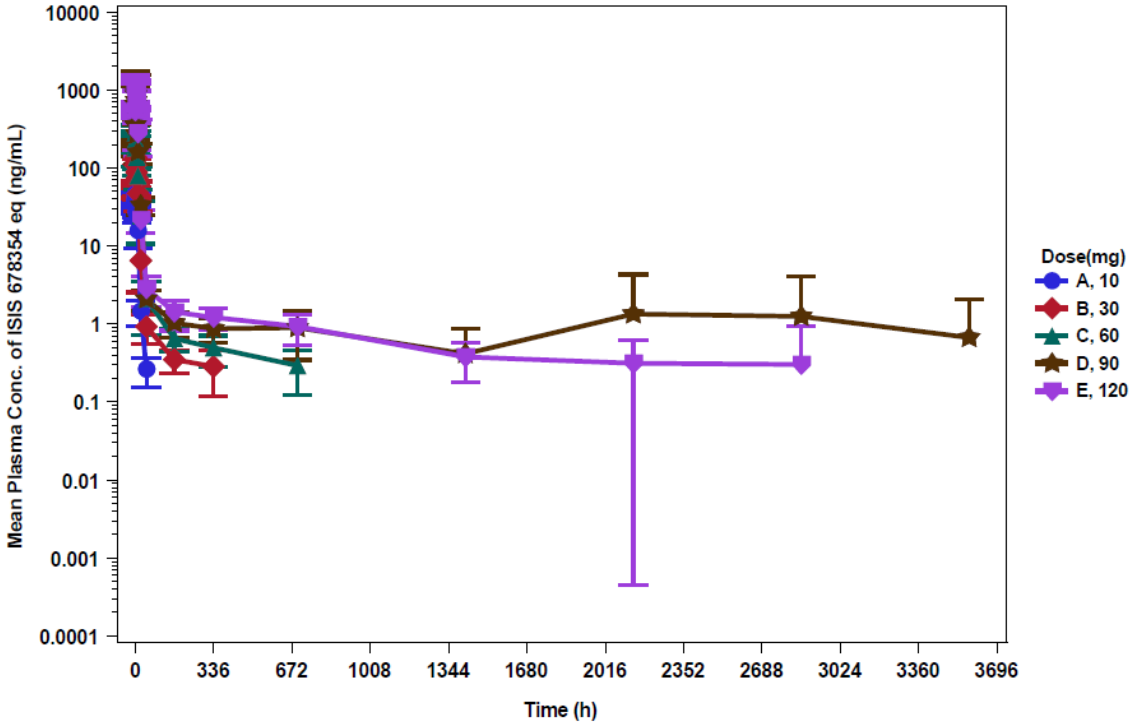
In Study ISIS 678354-CS1 ISIS 678354 exposure increased proportionally with dose in the dose range of 10 to 60 mg, and greater than dose proportionally from 60 to 120 mg. The elimination half-life of ISIS 678354 in plasma was approximately 3 to 6 weeks. The PK appeared to be dose-proportional at doses ranging from 10 mg to 60 mg. A slight trend was observed at doses ≥ 90 mg, suggesting a greater than dose-proportional increase in exposure, however, there were smaller numbers of participants (n = 12) in these groups (678354-PPK02 study).

Olezarsen is rapidly absorbed into the systemic circulation, with peak plasma levels observed at approximately 2 hours post-dose after subcutaneous administration. Absolute/relative bioavailability after subcutaneous administration of olezarsen has not been determined.



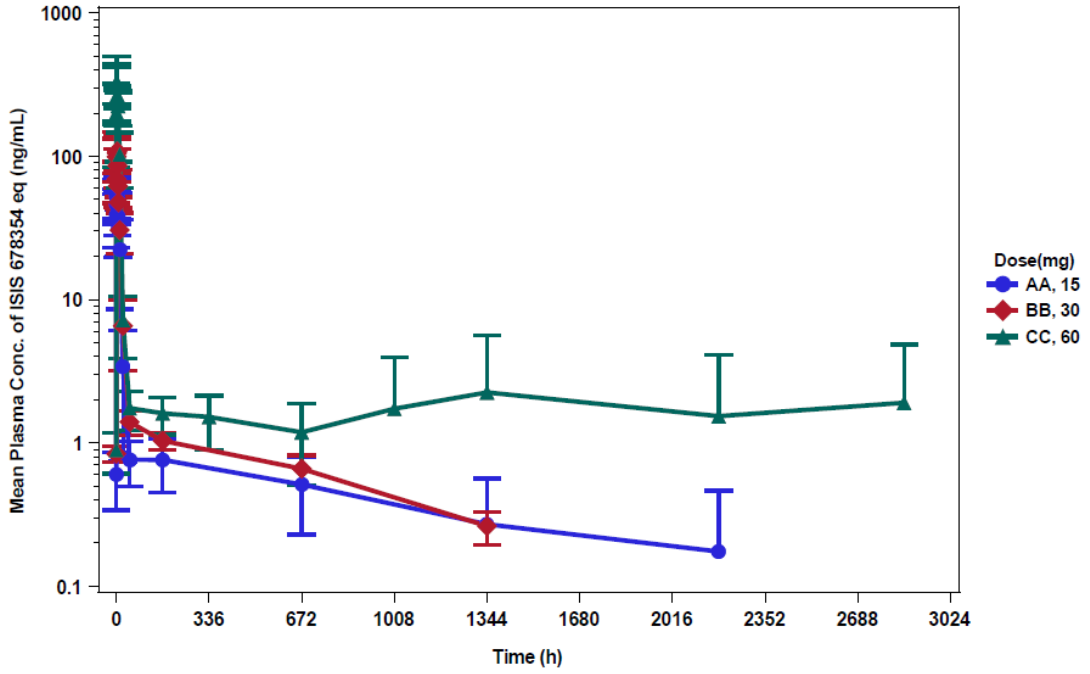
Abbreviations: Conc. = concentration; CSR = clinical study report; h = hour; ISIS 678354 eq = olezarsen equivalent; SD = standard deviation

Figure 2: Mean (±SD) Plasma Concentrations of Olezarsen vs. Time up to 24 Hours by Dose Following Single Subcutaneous Administration in the Single-Dose Cohorts in Study ISIS 678354-CS1



Abbreviations: Conc. = concentration; CSR = clinical study report; h = hour; ISIS 678354 eq = olezarsen equivalent; SD = standard deviation

Figure 3: Mean (±SD) Plasma Concentrations of Olezarsen vs. Time (Full Profile) by Dose Following Single Subcutaneous Administration in the Single-Dose Cohorts in Study ISIS 678354-CS1



Abbreviations: Conc. = concentration; CSR = clinical study report; h = hour; ISIS 678354 eq = olezarsen equivalent; SD = standard deviation

Figure 4: Mean (±SD) Plasma Concentrations of Olezarsen vs. Time Following the Last Subcutaneous Dose Administration on Day 36 (Weekly) or Day 85 (Every 4 Weeks) in the Multiple-Dose Cohorts in Study ISIS 678354-CS1

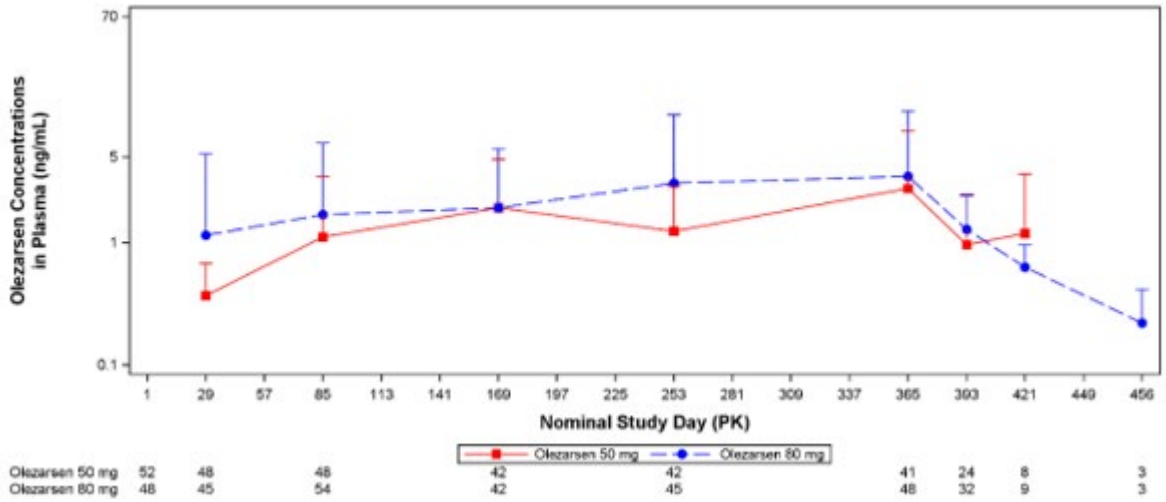
Mean ISIS 678354 plasma concentrations decreased greater than 90% from the C_{max} by 24 hours after SC injections. After single and weekly SC doses in the range of 15 to 30 mg, the C_{max} and AUC increased approximately dose proportionally. No accumulation in plasma C_{max} or AUC values was observed after weekly or Q4W doses, consistent with comparable PK profiles after single and repeat doses.

Table 1: Plasma Pharmacokinetic Parameters of ISIS 678354-Equivalent After Single and Multiple SC Administration in Healthy Subjects

Dose	Study Day	n	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng*h/mL)	AUC_{0-48h} (ng*h/mL)	AUC_{0-168h} or AUC_{0-672h} (ng*h/mL)	CL_{ss}/F (L/h)	$t_{1/2}$ (day)
15 mg QW	1	6	72.3 (50.1)	2.50 (1.00-4.00)	691 (36.4)	728 (34.9)	762 (35.8)	NC	NC
	36	6	55.0 (36.5)	3.00 (1.00-6.00)	564 (43.0)	611 (42.9)	699 (41.7)	21.5 (41.7)	40.3 (109.1)
30 mg QW	1	7	128 (26.2)	1.00 (0.533-4.00)	1210 (10.0)	1290 (10.6)	1340 (11.3)	NC	NC
	36	6[a]	113 (30.8)	2.00 (1.50-3.00)	993 (17.0)	1090 (15.8)	1230 (14.9)	24.3 (14.9)	25.2 (17.0)
60 mg Q4W	1	6	418 (45.5)	1.50 (1.00-3.00)	3210 (28.0)	3310 (27.4)	3680 (26.3)	NC	29.5 (46.8)
	85	4[b]	359 (36.6)	1.50 (1.00-3.00)	3130 (23.9)	3240 (23.5)	4110 (25.8)	14.6 (25.8)	43.3[c] (9.5)

Abbreviations: AUC0-24h = area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-48h = AUC from time 0 to 48 hours; AUC0-168h = AUC from time 0 to 168 hours, reported for weekly dose groups equivalent to AUC0-tau over a 7-day dosing interval; AUC0-672h = AUC from time 0 to 672 hours, reported for every 4-week dose group equivalent to AUC0-tau over a 28-day dosing interval; CLss/F = apparent plasma clearance at steady state after SC administration, calculated as SC dose divided by AUC0-168h or AUC0-672h; Cmax = maximum plasma concentration; n = number of observations; NC = not calculated; SC = subcutaneous; t1/2 = terminal elimination half-life; Tmax = time of maximum plasma concentration Data presented are geometric mean (geometric mean coefficient of variation, CV%) except Tmax, which is presented as median (minimum-maximum). a One subject discontinued treatment after the third dose on Day 15. b One subject discontinued treatment after the third dose on Day 57; another subject withheld dose on Day 85 and received the fourth dose on Day 113. c t1/2 was calculated when appropriate data existed for characterization of the terminal elimination phase. The number of t1/2 values was smaller (n=3 for 60 mg Q4W on Day 85) compared to other parameters.

In the ISIS 678354-CS8 study it was shown that mean plasma olezarsen trough concentrations increased throughout the entire Treatment Period, and were dose-dependent, with higher mean levels in the olezarsen 80 mg group compared with the olezarsen 50 mg group.



Note: Analysis based on data collected while study drug was administered until the day of the patient's last contact date within the study. Note: If trough plasma concentration was below the LLOQ, where LLOQ = 0.130 ng/mL for olezarsen, it was treated as zero in calculating descriptive statistics. If the summary mean was below the LLOQ, it was presented as BLQ, and the SD, %CV, geometric mean, and geometric %CV were reported as not applicable. Note: Samples were excluded from descriptive statistics if there were large deviations between scheduled and actual sampling times (percent difference between scheduled and actual sampling time greater than 30%), or large deviations between actual dose and nominal dose (percent difference between nominal and actual dose greater than 30%). Note: At Nominal Study Day 456, the mean concentration in the olezarsen 50 mg group (N=3) was BLQ, resulting in no data point on Study Day 456 for the olezarsen 50 mg group. Abbreviations: BLQ = below the limit of quantification; LLOQ = lower limit of quantification; %CV = percent coefficient of variation; PK = pharmacokinetic; SD = standard deviation

Figure 5: Mean (+SD) Olezarsen Trough Plasma and Post-treatment Concentrations (ng/mL) by Treatment Group over Time (Semi-logarithmic Scale) – PK Set

Table 2: Olezarsen Trough and Post-treatment Plasma Concentrations (in ng/mL) by Anti-drug Antibody Category (PK Set)

Treatment	Visit	Nominal Time Point	Nominal Time (h)	Statistics	Negative ADA OLE50 (N=30) OLE80 (N=28)	Treatment-Unaffected ADA OLE50 (N=4) OLE80 (N=6)	Treatment-Emergent ADA OLE50 (N=24) OLE80 (N=23)	ADA Status Combined OLE50 (N=58) OLE80 (N=57)
Olezarsen 50 mg	Week 1 Day 1	Pre-dose	0	n	27	4	21	52
				Mean (SD)	0.000 (NA)	0.000 (NA)	0.000 (NA)	0.000 (NA)
				Median	0	0	0	0
				Min, Max	0.00 - 0.00	0.00 - 0.00	0.00 - 0.00	0.00 - 0.00
				Geom. Mean (Geom. %CV)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
	Week 5 Day 29	Pre-dose	672	n	27	3	18	48
				Mean (SD)	0.426 (0.393)	0.396 (0.171)	0.280 (0.120)	0.369 (0.311)
				Median	0.287	0.350	0.233	0.284
				Min, Max	0.00 - 1.62	0.25 - 0.59	0.14 - 0.63	0.00 - 1.62
				Geom. Mean (Geom. %CV)	NA (NA)	0.373 (44.329)	0.26 (40.095)	NA (NA)
	Week 25 Day 169	Pre-dose	672	n	20	3	19	42
				Mean (SD)	1.747 (2.999)	0.517 (0.212)	2.328 (2.934)	1.922 (2.861)
				Median	0.628	0.432	1.030	0.685
				Min, Max	0.00 - 10.80	0.36 - 0.76	0.27 - 10.90	0.00 - 10.90
				Geom. Mean (Geom. %CV)	NA (NA)	0.491 (40.196)	1.232 (164.578)	NA (NA)
Olezarsen 80 mg	Week 1 Day 1	Pre-dose	0	n	24	5	19	48
				Mean (SD)	0.000 (NA)	0.000 (NA)	0.000 (NA)	0.000 (NA)
				Median	0	0	0	0
				Min, Max	0.00 - 0.00	0.00 - 0.00	0.00 - 0.00	0.00 - 0.00

Treatment	Visit	Nominal Time Point	Nominal Time (h)	Statistics	Negative ADA OLE50 (N=30) OLE80 (N=28)	Treatment-Unaffected ADA OLE50 (N=4) OLE80 (N=6)	Treatment-Emergent ADA OLE50 (N=24) OLE80 (N=23)	ADA Status Combined OLE50 (N=58) OLE80 (N=57)
				Geom. Mean (Geom. %CV)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
	Week 5 Day 29	Pre-dose	672	n	23	4	18	45
				Mean (SD)	0.456 (0.203)	7.594 (13.740)	0.582 (0.600)	1.141 (4.146)
				Median	0.395	0.889	0.378	0.397
				Min, Max	0.22 - 0.96	0.40 - 28.20	0.15 - 2.69	0.15 - 28.20
				Geom. Mean (Geom. %CV)	0.418 (44.169)	1.7 (622.069)	0.43 (84.730)	0.479 (101.632)
	Week 25 Day 169	Pre-dose	672	n	17	5	20	42
				Mean (SD)	1.277 (0.753)	1.417 (0.462)	2.593 (5.604)	1.920 (3.901)
				Median	0.999	1.390	1.090	1.135
				Min, Max	0.57 - 3.74	0.74 - 2.01	0.17 - 26.00	0.17 - 26.00
				Geom. Mean (Geom. %CV)	1.140 (47.943)	1.347 (38.683)	1.227 (139.348)	1.204 (90.401)

Note: Analysis based on data collected while study drug was administered until the patient's last contact date. Note: If plasma concentration was BLQ (LLOQ, where LLOQ = 0.130 ng/mL for olezarsen), it was treated as zero in calculating descriptive statistics. If the summary mean was below the LLOQ, it was presented as BLQ, and the SD, and %CV, geometric mean, and geometric %CV were reported as not applicable. Note: Samples were excluded from descriptive statistics if there were large deviations between scheduled and actual sampling times (percent difference between scheduled and actual sampling time greater than 30%), or large deviations between actual dose and nominal dose (percent difference between nominal and actual dose greater than 30%). Treatment-Emergent ADA: both Treatment-Induced and Treatment-Boosted ADA-positive subjects. Treatment-Induced ADA: ADA developed de novo (seroconversion) following study drug administration (i.e., formation of ADA any time after the initial study drug administration in a subject without pre-existing ADA, i.e., Baseline-negative or Baseline-unknown

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 study drug administration, the ADA titer was 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 study drug administration, the ADA titer was 4-fold or less). Negative: All evaluated IM sample results during the treatment and post-treatment evaluation periods were negative and had at least 1 evaluable IM result collected after the first dose of study drug. If a subject had only a positive or unknown sample at Baseline (Study Day 1 pre-dose) and negative at all other time points, the subject was to have negative IM status. Abbreviations: ADA = anti-drug antibody; BLQ = below limit of quantification; Geom. = geometric; h = hours; IM = immunogenicity; LLOQ = lower limit of quantification; Max = maximum; Min = minimum; NA = not applicable; OLE50 = olezarsen 50 mg group; OLE80 = olezarsen 80mg group; %CV = percent coefficient of variation; PK = pharmacokinetic; SD = standard deviation.

A Single-Dose, Phase 1 Bioequivalence Study (ISIS 678354-CS20) was performed to compare two subcutaneous formulations: vial and autoinjector (AI) at two different dose levels of olezarsen (50 and 80 m), in healthy adult participants. This was a randomized, open-label, 2-period, 2-sequence, 2-treatment, 2-way crossover, bioequivalence study that evaluated 2 dose levels of olezarsen (50 mg and 80 mg). The primary objective of this study was to assess the bioequivalence of olezarsen between 2 subcutaneous injection formulations at 2 dose levels: (1) autoinjector (62.5 mg/mL, 0.8 mL) and vial (100 mg/mL, 0.5 mL) at 50 mg dose, and (2) autoinjector (100 mg/mL, 0.8 mL) and vial (100 mg/mL, 0.8 mL) at 80 mg dose, in healthy adult participants. Blood samples for the measurement of olezarsen plasma concentrations were collected at pre-dose, 0.5-, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 12-, 24-, 48-, 96-, 168-, and 336-hours post-dose. Bioequivalence for the new autoinjector products relative to vials was assessed based on the following criteria: the calculated 90% CIs for the ratio of GM for AUC0-336h and Cmax for olezarsen should fall within 80.00% to 125.00%. Results shows that the geometric mean ratio (GMR) 90% CI values for AUC0-336h were contained within the interval of 80.00% to 125.00% for both dose levels, meeting the standard acceptance criteria for bioequivalence for both comparisons (50 and 80 mg). For Cmax, the 90% CI of GMR for the autoinjector compared with the vial presentation were contained within the interval of 80.00% to 125.00% at the 50 mg dose level (GMR 116.07%; 90% CI: 108.63%, 124.02%), but exceeded the upper CI limit of 125.00% of the standard acceptance criteria for bioequivalence at the 80 mg dose level (GMR 118.94%; 90% CI: 108.83%, 129.99%), even after potency-corrected (i.e., delivered dose adjusted) adjustment.

678354-PPK02 study

Population estimates (mean ± SD) of steady state C_{max}, and AUC_{τ} were 883 ± 662 ng*h/mL and 7440 ± 3880 ng*h/mL, respectively, following 80 mg monthly dosing in patients with FCS. No accumulation of olezarsen C_{rax} and AUC was observed in repeated dosing (once every 4 weeks).

Table 3: Summary of Simulated PK Metrics at Steady-State (FCS Patients)

Regimen	N	Statistic	$AUC_{0-\tau,ss}$ (ng·h/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)	Accumulation Ratio AUC (-)	Accumulation Ratio C_{max} (-)	Accumulation Ratio C_{trough} (-)	$T_{1/2}$ (h)
30 mg Q1M	1000	N	1000	1000	1000	1000	1000	1000	1000
		Mean	2790	331	0.628	1.15	1.00	2.18	819
		SD	1450	248	0.551	0.131	0.00256	0.786	447
		CV%	52.1	75	87.6	11.4	0.3	36	54.6
		GeoMean	2460	262	0.446	1.14	1.00	2.07	729
		GeoMean CV%	53.6	78.5	105.5	10.4	0.3	32.7	50.2
		Min	303	20.8	0.0100	1.00	1.00	1.00	190
		Median	2460	266	0.480	1.11	1.00	2.00	721
		Max	11500	1940	4.42	2.25	1.02	7.43	5070
50 mg Q1M	1000	N	1000	1000	1000	1000	1000	1000	1000
		Mean	4650	552	1.05	1.15	1.00	2.18	821
		SD	2420	414	0.918	0.131	0.00255	0.785	448
		CV%	52.1	75	87.6	11.4	0.3	36	54.6
		GeoMean	4110	437	0.744	1.14	1.00	2.07	730
		GeoMean CV%	53.6	78.5	105.3	10.4	0.3	32.7	50
		Min	504	34.6	0.0200	1.00	1.00	1.00	199
		Median	4100	443	0.800	1.11	1.00	2.00	717
		Max	19200	3240	7.36	2.25	1.02	7.25	5170
50 mg Q4W	1000	N	1000	1000	1000	1000	1000	1000	1000
		Mean	4650	552	1.15	1.16	1.00	2.29	821
		SD	2420	414	0.994	0.135	0.00276	0.846	438
		CV%	52.1	75	86.7	11.7	0.3	36.9	53.3
		GeoMean	4110	437	0.821	1.15	1.00	2.17	732
		GeoMean CV%	53.6	78.5	103.2	10.7	0.3	33.5	49.8
		Min	504	34.7	0.0200	1.01	1.00	1.00	168
		Median	4100	443	0.890	1.12	1.00	2.10	717
		Max	19200	3240	7.97	2.29	1.02	7.83	3710
80 mg Q1M	1000	N	1000	1000	1000	1000	1000	1000	1000
		Mean	7440	883	1.68	1.15	1.00	2.18	821
		SD	3880	662	1.47	0.131	0.00255	0.785	452
		CV%	52.1	75	87.6	11.4	0.3	36	55.1
		GeoMean	6570	699	1.19	1.14	1.00	2.07	730
		GeoMean CV%	53.6	78.5	105.3	10.4	0.3	32.7	50.1
		Min	807	55.4	0.0300	1.00	1.00	1.00	202
		Median	6560	709	1.29	1.11	1.00	2.00	719
		Max	30700	5180	11.8	2.25	1.02	7.37	5570
80 mg Q4W	1000	N	1000	1000	1000	1000	1000	1000	1000
		Mean	7440	883	1.83	1.16	1.00	2.30	821
		SD	3880	662	1.59	0.135	0.00276	0.846	441
		CV%	52.1	75	86.7	11.7	0.3	36.9	53.7
		GeoMean	6570	699	1.31	1.15	1.00	2.17	731
		GeoMean CV%	53.6	78.5	103	10.7	0.3	33.4	49.8
		Min	807	55.4	0.0400	1.01	1.00	1.07	187
		Median	6560	709	1.43	1.12	1.00	2.09	719
		Max	30700	5180	12.8	2.29	1.02	7.95	4450
120 mg Q1M	1000	N	1000	1000	1000	1000	1000	1000	1000
		Mean	11200	1320	2.51	1.15	1.00	2.18	821
		SD	5820	994	2.20	0.131	0.00256	0.786	448
		CV%	52.1	75	87.6	11.4	0.3	36	54.6
		GeoMean	9860	1050	1.79	1.14	1.00	2.07	730
		GeoMean CV%	53.6	78.5	105.2	10.4	0.3	32.6	50
		Min	1210	83.2	0.0500	1.00	1.00	1.06	201
		Median	9840	1060	1.93	1.11	1.00	2.00	719
		Max	46000	7770	17.7	2.25	1.02	7.50	5150

Q1M = every month, Q4W = every four weeks.

Distribution

Olezarsen distributes primarily to the liver and kidney cortex after subcutaneous administration The population estimate of V_c/F and V_p/F were 91.9 L and 2960 L, respectively (678354-PPK02 study). Olezarsen is highly (> 99%) bound to human plasma proteins, with little change over a range of 5 to 150 µg/mL (Study No. 678354-IS04).

Accumulation in C_{trough} levels was observed following subcutaneous administration of 50 and 80 mg olezarsen once every 4 weeks. Based on the population PK model, the predicted accumulation in C_{trough} was ~ 2-fold and the population estimate of apparent terminal elimination half-life of approximately 4 weeks (678354-PPK02 study).

Table 4: Typical value of PK Metrics from the Final Population Model (678354-PPK02 study)

	$AUC_{0-\tau}$ (ng·h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	t_{max} (h)	Accumulation Ratio AUC	Accumulation Ratio C_{max}	Accumulation Ratio C_{trough}	$t_{1/2}$ (h)
Following First Dose	5325.544	606.97	0.633	2				
Steady-state	5984.66	608.3	1.33	2	1.124	1.002	2.1	720.565

A typical subject is defined as a healthy volunteer of White race receiving 80 mg olezarsen Q4W with a body weight of 70 kg, and vial as the drug presentation. Terminal half-life (t 1/2) was calculated as: t 1/2 = 0.693/k e , where k e is the first-order elimination rate constant. In brief, k e was estimated by linear regression of concentration versus time data presented in a semi-log scale. A minimum of three data points in the terminal phase were used in calculating k e with the line of regression starting with the final data point (that is not BLQ) and moving towards time zero. The number of data points used was determined by maximizing the value for the adjusted correlation coefficient (R2ad j) (>0.8).

Elimination

The primary route of elimination of olezarsen is initial rapid hydrolysis of GalNAc conjugate following uptake into tissues, and the unconjugated olezarsen (i.e., the ASO-moiety) is slowly metabolized by endo- and exonucleases. The population estimate of the terminal elimination half-life of olezarsen is approximately 30 days (approximately 4 weeks) (678354-PPK02 study). The slowly formed fragmented oligonucleotide metabolites were subsequently excreted in urine.

Urinary excretion of olezarsen was evaluated over a 24-hour period following subcutaneous injection in the single- (Day 1) and multiple-dose (Days 1 and 36 for once a week; Days 1 and 85 for once every 4 weeks) cohorts in healthy volunteers (Study ISIS 678354-CS1) and healthy Japanese volunteers (Study AKCEA-CS1).

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 both healthy volunteers and healthy Japanese volunteers, and was dose-independent in healthy volunteers, but increased with dose in healthy Japanese volunteers.

Metabolism

Olezarsen is an antisense oligonucleotide (ASO) not metabolized via classical CYP enzymes.

Oligonucleotide therapeutics are not typically metabolized by cytochrome P450 (CYP) enzymes. These drugs are primarily metabolized by endonucleases and exonucleases or are chemically modified to resist degradation.

Metabolite profiling of human plasma peak and trough samples at steady-state showed that there were no circulating olezarsen metabolites relative to total full-length oligonucleotides. The intact drug olezarsen being the major full-length oligonucleotide that appears in plasma after drug administration favours the intended ASGPR mediated hepatic uptake. Profiling of length-based oligonucleotide metabolites demonstrated that the only oligonucleotide species detected was intact olezarsen at the 2-hour time point, while trough samples following repeated once every 4 weeks doses of 60 mg olezarsen for 13 weeks (Day 85) were below the LLOQ (1 nM), as shown in 678354-IS09 and 678354-IS12 studies.

The full-length ASOs accounted for 100% of the total oligonucleotides present, when detected, and no shorter metabolites of olezarsen were detected in plasma at both time points evaluated.

Profiling of length-based oligonucleotide metabolites in urine samples indicates that numerous chain-shortened oligonucleotide metabolites were detected, in addition to olezarsen, following subcutaneous administration of a single 120 mg dose or 60 mg once every 4 weeks for 4 doses of olezarsen (Study No. 678354-IS09). The identified metabolites in urine are consistent with the ASO-moiety of olezarsen being metabolized by endo- and exonucleases in tissues.

Minimal linker-related metabolites were detected in human plasma, and when present, the highest levels typically presented at the 2-hour time point. However, concentrations of linker related metabolites in urine were substantially higher than in plasma (Study No. 678354 IS12). The minimal concentrations of linker-related metabolites observed in plasma over time suggest that linker-related metabolites are minimally released to circulation and subsequently rapidly excreted to urine.

There were no unique metabolites identified in humans compared with animal species.

Dose proportionality and time dependencies

In Study ISIS 678354-CS1, olezarsen exposure (C_{max} and AUC) increased in a dose-dependent manner at doses ranging from 10 to 120 mg see Study ISIS 678354-CS1 in 2.2.1 Absorption. The final population PKPD model that pooling PK data together from clinical studies of ISIS 678354-CS1, ISIS 678354-CS2, ISIS 678354-CS20, ISIS 678354-CS3, and AKCEA-CS1 was a two-compartment disposition model with simple first-order absorption and linear elimination process (678354-PPK02 study).

The C_{max} and AUC increased approximately proportionally with dose in the dose range of 10 to 60 mg, and greater than dose proportionally from 60 to 120 mg. After single and weekly SC doses in the range of 15 to 30 mg, the C_{max} and AUC increased approximately dose proportionally. No accumulation in plasma C_{max} or AUC values was observed after weekly or Q4W doses, consistent with comparable PK profiles after single and repeat doses (ISIS 678354-CS1 study).

Table 5: Plasma Pharmacokinetic Parameters of ISIS 678354-Equivalent After Single SC Administration in Healthy Subjects

Dose	n	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng*h/mL)	AUC_{0-48h} (ng*h/mL)	AUC_{last} (ng*h/mL)
10 mg	6	46.4 (21.0)	2.75 (1.00-4.02)	469 (14.8)	491 (13.4)	509 (13.3)
30 mg	6	132 (67.4)	1.75 (1.00-8.00)	1350 (41.5)	1460 (34.7)	1630 (37.5)
60 mg	6	284 (24.4)	1.00 (1.00-4.00)	2460 (17.9)	2780 (16.5)	3230 (21.5)
90 mg	6	1060 (81.0)	1.25 (1.00-4.00)	6270 (33.2)	6710 (30.9)	9280 (52.5)
120 mg	6	1160 (37.8)	2.01 (1.50-4.00)	9290 (39.4)	9610 (37.5)	11300 (41.7)

Abbreviations: AUC0-24h = area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-48h = AUC from time 0 to 48 hours; AUClast = AUC from time 0 to the time of last quantifiable concentration; CLlast/F = apparent plasma clearance from time 0 to the time of last quantifiable concentration after SC administration,

calculated as SC dose divided by AUClast; Cmax = maximum plasma concentration; n = number of observations; NC = not calculated; SC = subcutaneous; t1/2 = terminal elimination half-life; Tmax = time of maximum plasma concentration Data presented are geometric mean (geometric mean coefficient of variation, CV%) except Tmax, which is presented as median (minimum-maximum).

Table 6: Plasma Pharmacokinetic Parameters of ISIS 678354-Equivalent After Single and Multiple SC Administration in Healthy Subjects

Dose	Study Day	n	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng*h/mL)	AUC_{0-48h} (ng*h/mL)	AUC_{0-168h} or AUC_{0-672h} (ng*h/mL)
15 mg QW	1	6	72.3 (50.1)	2.50 (1.00-4.00)	691 (36.4)	728 (34.9)	762 (35.8)
	36	6	55.0 (36.5)	3.00 (1.00-6.00)	564 (43.0)	611 (42.9)	699 (41.7)
30 mg QW	1	7	128 (26.2)	1.00 (0.533-4.00)	1210 (10.0)	1290 (10.6)	1340 (11.3)
	36	6[a]	113 (30.8)	2.00 (1.50-3.00)	993 (17.0)	1090 (15.8)	1230 (14.9)
60 mg Q4W	1	6	418 (45.5)	1.50 (1.00-3.00)	3210 (28.0)	3310 (27.4)	3680 (26.3)
	85	4[b]	359 (36.6)	1.50 (1.00-3.00)	3130 (23.9)	3240 (23.5)	4110 (25.8)

Abbreviations: AUC0-24h = area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-48h = AUC from time 0 to 48 hours; AUC0-168h = AUC from time 0 to 168 hours, reported for weekly dose groups equivalent to AUC0-tau over a 7-day dosing interval; AUC0-672h = AUC from time 0 to 672 hours, reported for every 4-week dose group equivalent to AUC0-tau over a 28-day dosing interval; CLss/F = apparent plasma clearance at steady state after SC administration, calculated as SC dose divided by AUC0-168h or AUC0-672h; Cmax = maximum plasma concentration; n = number of observations; NC = not calculated; SC = subcutaneous; t1/2 = terminal elimination half-life; Tmax = time of maximum plasma concentration Data presented are geometric mean (geometric mean coefficient of variation, CV%) except Tmax, which is presented as median (minimum-maximum).

Impact of immunogenicity on PK

Olezarsen plasma PK parameters, including C_{max}, AUC, terminal elimination half-life, and apparent clearance, were generally similar between ADA-negative and ADA-positive patients with HTG and established CVD, or at high risk for CVD (Study ISIS 678354CS2). In addition, peak plasma olezarsen concentrations were comparable between the ADA-negative and ADA positive FCS patients (patients with treatment-unaffected or treatment-emergent ADA) (Study ISIS 678354CS3). 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 both patients with FCS and patients with HTG and established CVD or at high risk for CVD).

Special populations

The population PK analysis did not identify significant differences among healthy volunteers, patients with HTG and CVD, and patients with FCS. $C_{max,ss}$, $AUC_{tau,ss}$, and $C_{trough,ss}$ following subcutaneous administration of olezarsen 80 mg once every 4 weeks were found to be similar between healthy volunteers and patients with HTG and CVD, but slightly higher for patients with FCS than for healthy volunteers (geometric mean $C_{max,ss}$ of 696 vs. 473 ng/mL, and $AUC_{tau,ss}$ of 6340 vs. 5100 ng•h/mL and $C_{trough,ss}$ of 1.27 vs. 1.00 ng/mL, respectively) (Study 678354-PPK02).

The effects of intrinsic and extrinsic factors on the PK of olezarsen were evaluated in the population PK analysis. Olezarsen has not been studied in patients with severe hepatic impairment. Olezarsen has also not been studied in patients with severe renal impairment or in patients with ESRD. This is acceptable.

The population PK analysis did not find Baseline eGFR as a statistically significant covariate impacting olezarsen PK. The post-hoc estimates of steady state exposure, including C_{max}, AUC, and C_{trough} were similar among the normal renal function and mild and moderate renal impairment patients. However, the Pop PK analysis suggested an increase in olezarsen exposure with increased impairment of renal function, although data in patients with moderate renal impairment is limited (n=3). Post-hoc estimates of TG in this case, suggest an increase in effect with increasing degree of renal impairment and no dose modification is required. There is no data in patients with severe RI and ESRD and given that nephrotoxicity is being discussed as an important potential risk in the RMP, the applicant discussed the precautionary measures for this population and noted that in the SmPC.

The population PK analysis did not find Baseline AST, ALT, or bilirubin as statistically significant covariates impacting olezarsen PK. The steady state apoC-III reduction was similar between participants with normal hepatic function (N = 257) and participants with mild (N = 12) or moderate (N = 1) hepatic impairment. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Olezarsen has not been studied in patients with severe hepatic impairment.

Gender was not identified as a statistically significant covariate in the population PK analysis. No dose adjustment is needed among different genders.

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). No dose adjustment is needed based on race.

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 CL/F, Q/F, V_c/F, and V_p/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 10^{th} percentile of the body weight distribution, i.e., with a weight of 61 kg, is expected to have a 16%, 28%, and 9% increase, respectively. However, the steady state apoC-III and TG reductions (percent change from Baseline) were similar across different body weight groups. The applicant has provided additional data to support that no dose adjustment is needed based on weight and the issue was resolved.

Age was not identified as a statistically significant covariate in the population PK analysis.

Olezarsen's drug product presentation has impact on PK: both k_a and relative F were higher for autoinjector as drug product presentation compared with vial by 1.3- and 1.05-fold, respectively. Injection site was not identified as a statistically significant covariate in the population PK analysis.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	41/272	8/272	0/272

Pharmacokinetic interaction studies

No in vivo drug interaction studies were conducted.

Pharmacokinetics using human biomaterials

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. In vitro studies showed that olezarsen is not an inducer nor inhibitor of CYP-mediated oxidative metabolism, nor an inhibitor or substrate for major drug transporters.

2.5.2.2. Pharmacodynamics

Mechanism of action

Olezarsen targets apoC-III and treats FCS. Olezarsen is an antisense oligonucleotide (ASO). ASOs are short synthetic strings of nucleotides designed to prevent the expression of a targeted protein by selectively binding to the mRNA that encodes the target protein, thereby preventing translation. These compounds bind to RNA with high affinity and selectively through well-characterized Watson-Crick base pairing (hybridization). By inhibiting the translation of apoC-III mRNA by an ASO, apoC-III and serum triglyceride levels are reduced.

Olezarsen shows rapid (i.e., substantial decrease on Day 8 post first dose), dose-dependent, persistent, and long-lasting effect through and after treatment on the mean percent reductions from Baseline in apoC-III and TG among healthy volunteers (ISIS 678354-CS1 and AKCEA-CS1), patients with HTG and elevated CV risk (Studies ISIS 678354-CS2 and ISIS 678354-CS8) and patients with FCS (Study ISIS 678354-CS3). Mean apoC-III percent reductions from Baseline were slightly smaller in patients with HTG and ASCVD or FCS than in healthy volunteers. Mean TG percent reductions from Baseline were slightly smaller in patients with HTG and ASCVD than in healthy volunteers, and smaller in FCS patients than in healthy volunteers and patients with HTG and ASCVD. The long-lasting pharmacologic effect was consistent with the long elimination half-life of the drug, supporting the monthly dosing regimen. The PK/pharmacodynamics models were developed that well describe the observed apoC-III and TG reductions.

Primary and Secondary pharmacology

PD data were analyzed as the change and percent change from Baseline in serum apoC-III and TG levels in Studies ISIS 678354CS1, AKCEA-CS1, ISIS 678354-CS2, ISIS 678354-CS3, and ISIS 678354-CS8 following subcutaneous administrations of olezarsen. ApoC-III and TG showed substantial decrease on Day 8 after the start of olezarsen administration, was observed across all of the studies when Day 8 samples were collected and remained substantial up through the last day of the studies (up to 3 months after the last dose). The long-lasting pharmacologic effect was consistent with the long elimination half-life of the drug, supporting the monthly dosing regimen.

The reductions in apoC-III and TG were dose-dependent. For example, the mean percent reduction from Baseline at Day 30 after a single 10-, 30-, 60-, 90- or 120-mg dose of olezarsen was 17.5%,

31.0%, 57.8%, 72.3%, and 87.3%, respectively for apoC-III, and 12.3%, 4.4%, 38.4%, 60.2%, and 72.1%, respectively for TG (ISIS 678354-CS1). In healthy Japanese volunteers (Study AKCEA-CS1), the mean percent reduction from Baseline in apoC-III and TG at Day 30 were in general similar to that seen in healthy volunteers of non-Japanese, with the mean percent reduction from Baseline of 37.7%, 55.1%, 66.3%, respectively for apoC-III, and 29.0%, 47.2%, and 23.0%, respectively, for TG after a 30-, 60-, or 90-mg single olezarsen dose, (AKCEA-CS1 study). It was noted that the observed TG reductions were highly variable.

The mean apoC-III and TG reductions were persistent through and after treatment. For o example, in Study ISIS 678354CS1 (conducted in healthy volunteers), the maximum reduction from Baseline was reached at 83.1% for apoC-III and 64.6% for TG on Day 92 (7 days from the last dse) following the administration of olezarsen 60 mg once every 4 weeks, and remained as high as 44.1% for apoC-III and 40.0% for TG on Day 176 (13 weeks after the last dose) (ISIS 678354-CS1 study). Similarly in Study AKCEA-CS1 study (healthy subjects of Japanese descent), the maximum reductions from Baseline were reached at 81.7% for apoC-III and 74.8% for TG on Day 92 (7 days from the last dose) following the administration of olezarsen 60 mg once every 4 weeks, and they remained as high as 34.8% for apoC-III and 40.6% for TG on Day 176 (13 weeks after the last dose) (AKCEACS1 study).

The characteristics of apoC-III and TG reduction described for healthy volunteers above were also observed in patents with CVD and HTG (ISIS 678354-CS2 and ISIS 678354-CS8, respectively), and patients with FCS (ISIS 678354-CS3 study), with some variations on the magnitude of apoC-III and TG reductions.

Similar but slightly smaller apoC-III median percent reductions from Baseline were observed in patients (with FCS or HTG and CVD) compared with healthy volunteers. Model estimated maximum apoC-III median percent reductions from Baseline were 85.5% in healthy volunteers, 79.1% in patients with HTG and CVD, and 76.6% in FCS patients (678354-PPK02); the 95% CI of these apoC-III median percent reductions were within the 80% – 125% range.

TG median percent reductions from Baseline were similar in patients with HTG or CVD and healthy volunteers, and smaller in patients with FCS. Model estimated maximum TG median percent reductions from Baseline were 62.1% in healthy volunteers, 60.1% in patients with HTG and CVD, and 38% in patients with FCS (678354-PPK02); the 95% CI of fold change in maximum TG percentage reduction from Baseline was within the 80% – 125% range.

The studies conducted to date that included the assessment of olezarsen cardiac safety comprise an in vitro hERG channel study (678354-IS05 study), an in vivo safety pharmacology study (678354-AS03 study), 13- and 9-month repeat dose toxicity studies in cynomolgus monkeys (678354-AS02 study), and a first-in-human Phase 1 clinical study (Study ISIS 678354-CS1). Given this data it can be concluded that at a dose 1.5-times the maximum recommended dose for Tryngolza, clinically significant QTc interval prolongation was not observed in the studies.

Immunogenicity

The presence of anti olezarsen antibodies did not have any effect on apoCIII reduction in olezarsen-treated patients with HTG/sHTG or patients with FCS across olezarsen clinical studies (see Studies ISIS 678354CS8, ISIS 678354-CS3 CSR, ISIS 678354CS13, and ISIS 678354-CS7).

In the pivotal study in patients with FCS (ISIS 678354-CS3), the mean percent change in apoCIII over time by subject ADA category following 50 mg or 80 mg olezarsen administered once every 4 weeks for 52 weeks does not reveal a consistent difference in apoC-III reduction between ADA negative

patients and patients with treatment unaffected or treatment emergent ADAs in any of the treatment groups.

Lack of impact of ADA on apoC-III reduction was also observed in patients with HTG and established CVD or at high risk for CVD or sHTG in the placebo-controlled supportive Study ISIS 678354-CS8.

In FCS patients in the OLE Study (ISIS 678354-CS13) and in FCS patients previously treated with volanesorsen (ISIS 678354-CS7), the presence of ADA to olezarsen and/or volanesorsen had no apparent effect on apoC-III.

No clinically meaningful impact of treatment-unaffected or treatment-emergent ADA was observed on the overall treatment-emergent adverse event (TEAE) incidence, severity, or seriousness of TEAEs, incidence of adverse events of special interest (AESI), incidence of other AEs of interest (OAEI), or in laboratory test results.

Dose justification

The appropriateness of a fixed dose of 80 mg once monthly delivered by prefilled syringe with autoinjector, to be used in patients with FCS is supported by the favourable benefit/risk profile in patients with FCS (ISIS 678354-CS3), supplemented by the efficacy and safety profile in patients with HTG and established or increased risk of ASCVD, or with sHTG (Study ISIS 678354-CS8, the Phase 1 Study ISIS 678354-CS20, the population PK and PK/pharmacodynamics modeling and simulation, and the E-R analyses). In conjunction with the population PK and PK/pharmacodynamics simulations, this supports no dose adjustments are warranted with respect to age, sex, race, geographical region, injection site, or mild to moderate hepatic or mild to moderate renal impairment.

2.5.3. Discussion on clinical pharmacology

Olezarsen (also known as ISIS 678354 or AKCEA-APOCIII-LRx) is a GalNAc3 conjugated antisense oligonucleotide (ASO) inhibitor of the molecular target apolipoprotein C-III (apoC-III), a key regulator of triglyceride (TG) metabolism. Olezarsen was developed for the reduction of apoC-III protein and TG in patients with familial chylomicronemia syndrome (FCS) and other diseases of severe hypertriglyceridemia (sHTG). The summary of PK, PD, PK/PD, E-R relationship, and/or immunogenicity of olezarsen, QT/QTc prolongation potential is based on 3 completed Phase 1 clinical studies conducted in healthy volunteers (Studies ISIS 678354-CS1, AKCEA-CS1, and ISIS 678354-CS20), 2 Phase 2 studies in patients with hypertriglyceridemia (ISIS 678354 CS2 and ISIS 678354-CS8), a Phase 3, randomized, double-blind, placebo controlled study in patients with FCS (ISIS 678354-CS3), and two ongoing open-label safety studies (ISIS 678354 CS13 and ISIS 678354-CS7).

Bioanalytical methods

Pharmacokinetics methods

Two bioanalytical methods for measurement of olezarsen concentrations in plasma (ICD 624) or urine (ICD 624.3) were developed and validated.

- The method ICD 624 for the analysis of olezarsen in human plasma containing dipotassium EDTA was based on hybridization electrochemiluminescence (ECL). Validation performance was evaluated in report 678354-MV04 and addendum. As required by EMA guideline on Bioanalytical Method Validation, the ECL-based assay was found to be sufficiently accurate and precise to allow reliable determination of olezarsen in human plasma for pharmacokinetic (PK) studies, in a nominal range of 0.1500 nM

(1.303 ng/mL) to 20.00 nM (173.7 ng/mL). In clinical studies, the performance of the ICD 624 analytical method was considered acceptable.

- Hybridization ELISA method was used for measurement of olezarsen in human urine. In study report 678354-MV05 the assay was partially validated in compliance with EMA Guideline. The results showed that the method is suitable for the quantification of olezarsen in urine in the nominal concentration range of 0.1500 nM (0.1303 ng/mL) to 20.00 nM (173.7 ng/mL). The performance of the ICD 624.3 method met the acceptance criteria in clinical studies.

Pharmacodynamic methods

Pharmacodynamic (PD) methods included the quantification of the following biomarkers: Apolipoprotein CIII (apoC-III), triglycerides (TG), apolipoprotein B (apoB)-48, non-high-density lipoprotein cholesterol (non-HDL-C), total apoB, very-low-density lipoprotein cholesterol (VLDL-C), chylomicron-TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A (apoA)-1, lipoprotein (a) [Lp(a)]. Most PD methods have been developed and validated by the manufacturer (IVD). While apoC-III, TG and ApoB-48 assays have been successfully validated at Medpace reference laboratories. In clinical trials, the quality control results of apoC-III were acceptable.

Anti-drug antibodies methods

Bioanalytical ELISA methods were designed to detect the presence of anti-olezarsen or anti-volanesorsen antibodies in human plasma. Each method consisted of three components: (1) screen assay, which identified initial positive or negative samples; (2) confirmation assay, which assessed specificity of the screened positive samples; and (3) titration assay, which estimated the titre of anti-drug antibody (ADA) for the confirmed positive samples.

In study 678354-MV09, ELISA method detection of anti-olezarsen antibodies in human plasma was successfully validated according to EMA guideline and white papers. The performance of olezarsen ADA assay met the acceptance criteria when it was used to support the AKCEA-CS1, ISIS 678354-CS2, -CS3, -CS7, -CS8 and -CS13 clinical studies.

Validation parameters for the detection of anti-volanesorsen antibodies in human plasma by an ELISA method were shown in study 304801-MV09. According to EMA guideline, the ADA method showed adequate validation results. The method supported the ISIS 678354-CS7 study with acceptable performance.

No specific method has been developed for the detection of neutralizing antibodies. The applicant states that, since olezarsen exerts its biological activity at the intracellular level, any ADA cannot directly neutralize the binding of olezarsen to the human apoC-III mRNA. For this reason, the neutralizing potential of ADA has been evaluated from the combined ADA, PK, and PD data. These data showed that ADA had no impact on peak plasma exposure, although higher C_{trough} was observed in positive patients. ADA positivity had no clinically relevant impact on apoC-III and TG reductions.

Pharmacokinetics

The pharmacokinetic (PK) properties of olezarsen were evaluated in single and multiple doses (once every week, and once every 4 weeks) in healthy subjects and multiple doses (once every 4 weeks) in patients with FCS.

Absorption

Olezarsen has peak plasma levels observed at approximately 2 hours post-dose after subcutaneous administration, plasma concentrations declined rapidly during the distribution phase followed by a

much slower elimination during the post-distribution phase. As also shown in non-clinical studies in animals (mice and monkeys), the rapid plasma clearance is attributed to extensive distribution of olezarsen to tissues, resulting in the highest concentrations in liver (the target organ for Pharmacology), and the kidney. Olezarsen absolute bioavailability has not been determined.

Population estimates (mean ± SD) of steady state C_{max}, and AUC_{τ} were 883 ± 662 ng*h/mL and 7440 ± 3880 ng*h/mL, respectively, following 80 mg monthly dosing in patients with FCS.

The olezarsen's maximum concentration (C_{max}) and area under the curve (AUC) increase in dose-proportional manner after single subcutaneous doses ranging from 10 to 120 mg (i.e., 0.13- to 1.5-times the recommended dose) in healthy volunteers and no accumulation in plasma C_{max} or AUC values was observed after weekly or Q4W doses.

Bioequivalence

The olezarsen intended commercial formulation is 80 mg solution for injection in pre-filled pen, while in the clinical program the formulation used was the vial with syringe. For this reason, a Single-Dose, Phase 1 Bioequivalence Study (ISIS 678354-CS20) was performed to compare the two subcutaneous formulations (vial and autoinjector) at two different dose levels of olezarsen (50 and 80 mg), in healthy adult subjects.

The design of the study (2-period, 2-sequence, 2-treatment, 2-way crossover), as well as the wash out period is considered adequate, considering the short plasma half-life of olezarsen. However, it seems that that drug concentrations are not below the LLOQ (0.130 ng/mL) in all subjects at the beginning of the second period for both sequence A-B/B-A and C-D/D-C (tables 14.2.1.2, 14.2.1.3 and 14.2.1.3 of CSR ISIS 678354-CS20) as recommended in the relevant GL CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.

Results shows that the geometric mean ratio (GMR) 90% CI values for AUC0-336h were contained within the interval of 80.00% to 125.00% for both dose levels, meeting the standard acceptance criteria for bioequivalence for both comparisons (50 and 80 mg). For Cmax, the 90% CI of GMR for the autoinjector compared with the vial presentation were contained within the interval of 80.00% to 125.00% at the 50 mg dose level (GMR 116.07%; 90% CI: 108.63%, 124.02%), but exceeded the upper CI limit of 125.00% of the standard acceptance criteria for bioequivalence at the 80 mg dose level (GMR 118.94%; 90% CI: 108.83%, 129.99%), even after potency-corrected (i.e., delivered dose adjusted) adjustment.

The applicant justified these results on the basis of the higher intrasubject variability in Cmax versus AUC0-336h and on the basis of a small difference in delivered dose between the two pharmaceutical presentations (vial versus AI). Although these justifications are overall shareable and obviously the AUC is the main clinically relevant parameter, it is to be noted that there is also an effect period, with pre-dose concentration higher that LLOQ that might contribute to this deviation from BE margins.

Food effect studies are not applicable because olezarsen is administered subcutaneously.

Distribution, elimination, metabolism

No human mass balance study was performed that is considered acceptable due to the long elimination half-life and also considering results from mass balance studies in animals.

Olezarsen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing and is bound to human plasma proteins (> 99%) in vitro, has a volume of distribution of 91.9 L with apparent peripheral volume of distribution of 2960 L.

Olezarsen is eliminated via hydrolysis of GalNAc conjugate taken up into tissues, metabolized by endo- and exonucleases and has a terminal elimination half-life of olezarsen is approximately 30 days

(678354-PPK02 study). The metabolites are excreted in urine and 1% of the administered dose can be recovered in urine within 24 hours. The mass balance study was not conducted, and this is acceptable because olezarsen is an antisense oligonucleotide-triantennary N-acetylgalactosamine (GalNAc3).

Olezarsen is an antisense oligonucleotide (ASO) and as such is not typically metabolized by cytochrome P450 (CYP) enzymes. Profiling of length-based oligonucleotide metabolites in urine samples shows that numerous chain-shortened oligonucleotide metabolites can be detected. There are no unique metabolites identified in humans compared with animal species.

Olezarsen plasma PK parameters, including C_{max}, AUC, terminal elimination half-life, and apparent clearance, were generally similar between ADA-negative and ADA-positive.

Metabolite profiling of human plasma peak and trough samples at steady-state was evaluated in the context of study ISIS 678354-CS1. In plasma, the full-length ASOs accounted for 100% of the total oligonucleotides present, and no shortmer metabolites of olezarsen were detected at Day 1 and Day 85 following either single-dose or repeat-dose administration. The recovery of full-length ASO in urine is very limited (< 1% of administered dose over a 24-hour period), suggesting and confirming that clearance from plasma occurred primarily by distribution to tissues, where the drug is metabolized to chain-shortened oligonucleotide metabolites prior to renal excretion

Also, olezarsen linker-related metabolism was evaluated in plasma and urine. There were 8 linker-related metabolites in human plasma and their concentration were < 1% of parent drug, while in urine, concentrations of linker-related metabolites are higher than in plasma but overall accounted for approximately 9% of the administered dose.

Pharmacokinetics in special populations

The effects of intrinsic and extrinsic factors on the PK of olezarsen were evaluated in the population PK analysis. In addition, individual post-hoc PK metrics were summarized and stratified by intrinsic and extrinsic factors.

The population PK analysis did not identify significant differences among healthy volunteers, patients with HTG and CVD, and patients with FCS.

The population PK analysis did not find Baseline eGFR as a statistically significant covariate impacting olezarsen PK. The post-hoc estimates of steady state exposure, including C_{max}, AUC, and C_{trough} were similar among the normal renal function and mild and moderate renal impairment patients. Olezarsen was not studied in patients with severe renal impairment or with ESRD. However, the Pop PK analysis suggested an increase in olezarsen exposure with increased impairment of renal function, although data in patients with moderate RI is limited (n=3). Post-hoc estimates of TG in this case, suggest an increase in effect with increasing degree of renal impairment and no dose modification is required. There is no data in patients with severe RI and ESRD and given that nephrotoxicity is being discussed as an important potential risk in the RMP, the applicant was asked to discuss precautionary measures for this population and this in now addressed in the SmPC and the issue was resolved.

The population PK analysis did not identify Baseline AST, ALT, or bilirubin as statistically significant covariates impacting olezarsen PK. The steady state apoC-III reduction was similar between participants with normal hepatic function (N = 257) and participants with mild (N = 12) or moderate (N = 1) hepatic impairment. Moreover, the range of post-hoc estimates of steady-state exposure (C_{max}, AUC, and C_{trough}) were overlapping between participants with normal hepatic function and participants with mild or moderate hepatic impairment (based on NCI-ODWG classification category).

Although a popPK modelling approach to evaluate the impact of HI on the PK/PD profile has been in general considered acceptable for other ASO since these products do not undergoes liver metabolism but are degraded by exo- and endonuclease, it is of note that liver is the target organ for olezarsen,

being ASGPR mainly expressed in the liver and some literature data show that under certain conditions, this receptor could be over-expressed or downregulated.

Particularly, Guohua An et al, 2024 reported that the hepatic expression of ASGPR may be significantly impacted by liver disease. Witzigmann et al 2016 reported that ASGR1, the major receptor subunit, is upregulated in cirrhosis and is significantly decreased in hepatocellular carcinoma.

Despite from other papers (i.e. Willoughby JLS, et al 2018) it seems that in preclinical animal models a reduction of the expression of the ASGPR receptor of 50% does not affect the efficacy, it is not fully elucidated what happens at safety level. In case of ASGPR reduced expression there will be increases in plasma concentration of not receptor binding drug and maybe an increase of off-target effects. Of note, at present, in the olezarsen dossier, non-clinical studies that exclude significant off-target effects were only conducted in animals with normal liver function.

In addition, the FDA GL on ASO reports: <... When the oligonucleotide therapeutic targets the liver, i.e., the pharmacological target is in the liver or there is active targeting to the liver, the sponsor should consider characterizing the impact of hepatic impairment.><...Because changes in organ function can result in pharmacodynamic changes that are not reflective of pharmacokinetic changes, whenever appropriate and feasible, the sponsor should conduct pharmacodynamic assessments. When appropriate, population pharmacokinetic-pharmacodynamic modeling can help assess the correlation between organ impairment and pharmacodynamics, other biomarkers, safety, or efficacy data...>.

In conclusion, although a PopPK model was run to describe the impact of olezarsen on mild and moderate hepatic impaired subjects, it seems that only HEPATC mild hepatic impairment on Imax has been evaluated. Moreover, only 12 participants with mild hepatic impairment a 1 patient with moderate hepatic impairment have been enrolled in clinical studies and no investigation was performed on severe HI. Considering that liver is the main target of this drug, a justification was expected to better elucidate whether a contraindication should be considered, or alternative measures should be taken in severe HI and moderate HI. No additional information about this issue have been provided in responses to d120 LoQ, however, the applicant proposes a new text in section 4.2 (and 5.2) of the SmPC to mitigate the absence of conclusive information on hepatic impairment categories. The applicant has also informed the Agency that the applicant is currently planning to initiate a study to evaluate olezarsen in patients with moderate hepatic impairment (i.e., clinical study ISIS 678354-CS22). Overall, this approach, together with the amendment of specific section of the SmPC is considered acceptable. The study in patients with moderate hepatic impairment was included as a post-approval recommendation (REC).

Gender was not identified as a statistically significant covariate in the population PK analysis.

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). No dose adjustment is needed on the basis of race.

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 CL/F, Q/F, V_c/F, and V_p/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 10^{th} percentile of the body weight distribution, i.e., with a weight of 61 kg, is expected to have a 16%, 28%, and 9% increase, respectively. However, the steady state apoC-III and TG reductions (percent change from Baseline) were similar across different body weight groups. The E-R analysis also shows that the differences in $C_{max,ss}$ and $C_{trough,ss}$ do not translate to clinically meaningful differences in apoC-III and TG reduction,

efficacy, or safety. The applicant explained the impact of body weight on PK and posology and discussed a potential dose increase for subjects with low body weight and it was concluded that no dose adjustment is needed. Age was not identified as a statistically significant covariate in the population PK analysis.

Olezarsen's drug product presentation has impact on PK: both k_a and relative F were higher for autoinjector as drug product presentation compared with vial by 1.3- and 1.05-fold, respectively. The applicant has also shown that the reductions in apoC-III and TG were similar between autoinjector and vial groups, thus, it can be concluded that different drug product presentation is unlikely to have significant impact on posology or benefit/risk ratio. Injection site was not identified as a statistically significant covariate in the population PK analysis.

PopPK analyses

A Population Pharmacokinetics Analysis of Olezarsen has been performed with the main objectives to:

1) develop a population pharmacokinetic (PK) model of olezarsen using data from studies ISIS 678354-CS1, AKCEA-CS1, ISIS 678354-CS20, ISIS 678354-CS2, and ISIS 678354-CS3;

2) develop a population pharmacokinetic-pharmacodynamic (PKPD) model of olezarsen using data from studies ISIS 678354-CS1, AKCEA-CS1, ISIS 678354-CS20, ISIS 678354-CS2, and ISIS 678354-CS3;

3) conduct simulations using the final models to support Phase 3 dose selection.

Olezarsen PK and pharmacodynamic (PD) data (i.e., apolipoprotein C-III [apoC-III] and triglycerides [TG]) were sourced from studies ISIS 678354-CS1, AKCEA-CS1, ISIS 678354- CS20, ISIS 678354-CS2, and ISIS 678354-CS3.

The population PK analysis was based on the pooled dataset containing a total of 8020 PK samples available from 379 participants in clinical studies.

The final modelling dataset included a total of 5486 PK observations from 277 subjects (HV and patients) from phase 1, phase 2 and phase 3 studies. The dataset includes a wide range of doses, from 10 mg up to 80 mg (single dose and/or Q4W), administered subcutaneously.

The final population PK model (678354-PPK02 study) was a 2-compartment disposition model with simple first-order absorption and linear elimination process. Model diagnostics of the final model for both goodness of fit and simulation properties, as assessed by visual predictive checks. The population PK covariate analysis identified body weight, Japanese race, and drug product presentation (autoinjector vs. vial) as statistically significant covariates. Specifically, body weight was identified as a covariate on CL/F, Vc/F, Q/F, Vp/F, and ka with exponents estimated for each of these parameters. This pop PK model was later used to conduct PK/PD analysis (see 2.4 Pharmacokinetics-Pharmacodynamics (PK/PD)). In principle the pop PK and PK/PD analyses were conducted in line with current guidelines (CHMP/EWP/185990/06) and received scientific advice (EMA/CHMP/SAWP/318076/2020).

The estimates of the final model show that all model parameters were estimated reasonably well with RSE ≤30% and random effects shrinkage was acceptable (< 30%) except for Ka. Random effects were normally distributed and unbiased. Model fit, evaluated with CWRES, individual plots, and ETA distribution plots, was generally unbiased with some exceptions. In particular, diagnostic plots of observed olezarsen concentrations versus individual model predicted concentrations show that data are evenly distributed about the line of identity, however a trend of underprediction at lower concentration can be seen in the plot of individual observations versus population predicted concentration.

Conditional weighted residuals (CWRES) vs. time since first dose and vs. population prediction indicate that data are randomly scattered around zero, with a slight deviation from the line of identity in the CWRES vs Time after last dose starting from 1500 hours after last dose, probably due to a lowering in the number of subjects and consequently of samples.

QQ plots of the distribution of Weighted residuals follow the line of identity indicating that CWRES is normally distributed with minimal deviations.

The applicant has provided VPC plots and overall, they seem to suggest that the model describe reasonably well the median observed data, with a slightly underprediction of low concentrations and on the contrary a slightly overprediction of high concentrations (5 and 95% percentiles). In 678354-PPK02 study VPC for healthy volunteers likely shows that the model underpredicts variability at later time points (e.g. week 18) and this is even more visible in VPC for HTG or CVD patients from week 36 up to week 66. The applicant needed to resubmit the corrected VPC plots where it would be clearly shown that blue shaded areas e.g. represent predicted concentrations, red areas – observed concentrations like in examples Bergstrand M. et al. 2011. The applicant has provided updated prediction-corrected visual predictive checks for performed nonlinear mixed-effects models in line with previous comments and reflect if model misspecification can have impact on chosen posology and the issue was resolved.

Separate population PKPD models were built for apoC-III and TG based on the final popPK model. Specifically:

1. An indirect response model was fitted initially to describe the relationship between olezarsen concentration and apoC-III, where the drug effect was specified as an inhibitory effect on production.

2. A separate indirect response model was fitted initially to describe the relationship between olezarsen concentration and TG, where the drug effect was specified as a stimulatory effect on elimination.

Final population PKPD models for apoC-III

A total of 277 individuals provided 2851 apoC-III concentrations to the analysis. The following intrinsic and extrinsic factors were evaluated for possible impact on the PD response: body weight, age, sex, race, region, observed Baseline TG, observed Baseline apoC-III, hepatic impairment status, and disease status. Among these factors, the population PK/PD analysis identified disease status as the only statistically significant covariate on apoC-III PD model parameters.

Specifically, disease status was included as a covariate on Kout and IC50, however, the impact of disease status on the maximum apoC-III percent change-from-Baseline over the steady-state dosing interval for the of 80 mg olezarsen Q4W was not statistically significant.

Diagnostic plots of observed olezarsen concentrations versus individual model predicted apoC-III concentrations show that data are evenly distributed about the line of identity, however a trend of slight underprediction at lower concentration and over prediction at higher concentration can be seen in the plot of individual observations versus population predicted apoC-III concentration. Distributions of Random Effects from the Final Population PKPD Model show that BSV terms appear to be normally distributed.

Conditional weighted residuals (CWRES) vs. time since first dose and vs. population prediction indicate that data are randomly scattered around zero.

QQ plots of the distribution of Weighted Residuals follow the line of identity indicating that CWRES is normally distributed.

Individual estimates of shrinkage for Kout and IC50 were 33.9% and 5.7%, respectively.

VPCs were stratified by disease status and suggest that the models adequately described the observed apoC-III concentrations in patients with FCS, at median values with high variability in predicting data at 95° percentile (higher apoC-III concentration), but overall observed data are contained within the 5° and 95° percentile of simulated data. Some miss-prediction can be observed for HV plot at later time points (from week 18) and for HTG or CVD patients plots from week 32 up to week 66, probably due to less data included in the model for these population at that time points.

Final population PKPD models for TG

A total of 277 individuals provided 3006 TG concentrations to the analysis.

The following intrinsic and extrinsic factors were evaluated for possible impact on the PD response: body weight, age, sex, race, region, observed Baseline TG, observed Baseline apoC-III, hepatic impairment status, and disease status. Among these factors, the population PK/PD analysis identified disease status as the only statistically significant covariate on TG PD model parameters.

Specifically, disease status was included as a covariate on Kout and EC50. The impact of disease status on the maximum TG percent change-from-Baseline over the steady-state dosing interval was evaluated.

TG mean percent reduction from Baseline over the steady-state dosing interval at Ctrough was predicted to be 3% more for patients with HTG or CVD, and 52% less for patients with FCS.

Diagnostic plots of observed olezarsen concentrations versus individual model predicted TG concentrations show that data are evenly distributed about the line of identity, however a trend of slight underprediction at lower concentration and over prediction at higher concentration can be seen in the plot of individual observations versus population predicted TG concentration.

Distributions of Random Effects from the Final Population PKPD Model show that BSV terms appear to be normally distributed. Conditional weighted residuals (CWRES) vs. time since first dose indicate that data are randomly scattered around zero, while CWRES vs. population prediction indicate a deviation from the line of identity, meaning that there are some bias in the residual error model. Also QQ plots of the distribution of weighted residuals skewed from the line of identity indicating that CWRES are not normally distributed.

Individual estimates of shrinkage for Kout and Emax were high 51.8% and 55%, respectively, while it is below 30% for EC50 (19.1%).

VPCs were stratified by disease status and suggest that the models adequately described the observed TG concentrations in patients with FCS, at median values, while a slight miss-prediction with high variability in predicting data at 95° percentile (higher TC concentration) was observed. Overall, for FCS plots, observed data are contained within the 5° and 95° percentile of simulated data. Some miss-prediction can be observed for HV plot and for HTG or CVD patients' plots at later time points.

Overall, considering the low impact of PK/PD model in the B/R balance of olezarsen, the diagnostic performance could be considered acceptable.

The proposed simulations in paediatric patients with FCS aged 12 to 17 years based on simulations from the previously developed population PKPD model are acceptable (Supplement I to Report 678354-PPK02). However, A PIP waiver for paediatric population from birth to less than 2 years of age and a deferral for the population from 2 years to less than 18 years of age in the treatment of FCS was approved by EMA on 31 January 2023 (EMEA-003177-PIP01-21).

<u>Drug interactions</u>

PK interactions

In vitro studies showed that olezarsen is not an inducer nor inhibitor of CYP-mediated oxidative metabolism, nor an inhibitor or substrate for major drug transporters. No significant drug-drug interaction was observed in vitro and, thus, no-vivo drug interaction study was conducted. This is acceptable and in line with received scientific advice (EMA/CHMP/SAWP/318076/2020).

No clinical evidence has been provided in terms of possible interaction between olezarsen and other lipid-lowering drugs that could be commonly concomitantly used in FCS patients. However, the applicant further evaluated, through the final popPK model, the possible influence of concomitant use with fibrates, lipid modifying agents, HMG CoA reductase inhibitors, platelet aggregation inhibitors excluding heparin and anti-diabetics. On the basis of the presented plots of the individual eta values vs concomitant medication covariates, an impact of the mentioned concomitant medicines on olezarsen PK profile is not expected.

The recommended dosage of olezarsen is 80 mg administered by subcutaneous injection once monthly, (also supported by popPK simulations 80 mg monthly dose) provided the following exposure (medians): AUC 5810 $_{0\text{-tau}}$ ng*h/mL, C $_{max}$ 706 ng/ml, C $_{through}$ 0.615 ng/ml after first dose and AUC $_{0\text{-tau}}$ 6560 ng*h/mL and C $_{max}$ 709 ng/ml, C $_{through}$ 1.29 ng/ml in steady state (678354-PPK02 study). However, in Study ISIS 678354-CS8 in patients with HTG and ASCVD or with sHTG, increases in ALT, AST, and dose dependant decrease from Baseline platelet count were observed by C_{max} with similar results by $C_{through}$.

Pharmacodynamics

Mechanism of action

Olezarsen is an antisense oligonucleotide (ASO) that targets apoC-III and treats FCS by reducing apoC-III and serum triglyceride levels.

Primary and secondary pharmacology

Olezarsen reduces apoC-III and TG levels in dose-dependent manner in healthy volunteers (Study ISIS 678354-CS1 and AKCEA CS1), patients with HTG and CVD (Study ISIS 678354-CS2, and ISIS 678354-CS8) and patients with FCS (Study ISIS 678354-CS3). TG mean percent reductions from Baseline were similar in healthy volunteers and in patients with HTG and CVD but smaller in patients with FCS. However, no titration of apoC-III encoding mRNA as direct target of olezarsen and relevant change from baseline following the treatment were carried-out on clinical samples; however non-clinical in silico and in vitro analyses together with above mentioned clinical titration of plasma apoC-III and TG adequately support olezarsen mechanism of action and its selectivity for the target mRNA, this is overall acceptable. According to available literature [Janas MM et al., 2018], in general, off-target interactions with mRNA different from the claimed target by ASOs cannot be totally excluded. In non-clinical analyses (i.e. 23-133f study) some off-target interactions were found for olezarsen. To further investigate such findings, the applicant further provided evidences excluding possible off-target binding and downregulation at least for transcripts relevant to human genes encoding for cell adhesion molecule 1 (CADM1) major isoforms, forkhead box P2 (FOXP2) and RAC1P2. Such genes were chosen since their sequence similarity with olezarsen.

In line with other ASOs, for olezarsen a delayed onset of pharmacodynamic effect with respect to plasma exposure peak can be observed, with a consequent prolonged duration of action [Guohua An, 2023]. Overall, reduction from baseline in both apoC-III and triglycerides were clearly observable right after about a week from the start of treatment with olezarsen. Although with some variations in magnitude between healthy subject and patients with HTG+CVD or FSC, such % decrease was overall dose-dependent and persisted all over the multiple/repeated dose periods of relevant phase 1 (i.e. CS1, AKCEA-CS1), phase 2 (CS2) and phase 3 (CS3) studies, while a gradually slow increase towards original baseline levels was shown following the interruption of the treatment. As for other ASOs,

olezarsen demonstrates a delayed onset of pharmacodynamic effect following s.c. injection, followed by a prolonged duration of action. On the basis of popPK/PD model, estimated maximum TG and apoC-III median % reductions from baseline were about 62% and 85% in healthy subjects, 60% and 79% in patients with HTG and CVD and 38% and 77% in FCS patients, respectively. (see also paragraph popPK/PD)

Q-T prolongation

A thorough QT/QTc study was not conducted for olezarsen also following a waiver granted by FDA in 2023. This is acceptable also considering the absence of cardiac delayed repolarization already demonstrated for volanesorsen (i.e. olezarsen not conjugated with GalNac moiety) administered in a tQTc study as single supra-therapeutic 300 mg dose (i.v and s.c.). Also, current literature shows a minimal QT liability for GalNAc-conjugated siRNAs [Yu et al 2017; Guohua An., 2023]. However, to support lack of QTc prolongation by olezarsen, in vitro hERG potassium channel study IS0 and in vivo non-clinical safety pharmacology studies AS03 and AS02 results were provided. Cardiac safety was also investigated through ECG monitoring in several clinical studies (i.e. AKCEA-CS1, CS2, CS3, CS7, CS8 and CS13), in particular within phase 1 CS1 study, where a regression analysis of plasmatic OLEZ concentrations vs ΔQTcF showed no effect on QT interval at both therapeutic and supra-therapeutic doses (up to 120 mg single dose). Results were also confirmed through model-predicted ΔΔQTcF and estimated placebo-adjusted ΔQTcF (mean and 90% CI) up to a predicted plasma concentration of ~2880 ng/mL. Therefore, as for known ASOs, for olezarsen an effect on QTcF interval beyond ±10msec is not expected.

PK/PD analyses

The population PK/PD analysis was conducted with 4858 apoC-III observations from 379 subjects in the clinical Studies ISIS 678354-CS1, ISIS 678354-CS2, ISIS 678354-CS20, ISIS 678354-CS3, and AKCEA-CS1. The population PKPD modeling was performed in NONMEM where parameter estimates and SEs were achieved using importance sampling (IMP). Simulations were performed for the following scenarios: 50 mg olezarsen once every 4 weeks (Q4W) for 13 doses (364 days) or every month (Q1M) for 12 doses (360 days), 80 mg olezarsen Q4W for 13 doses (364 days) or Q1M for 12 doses (360 days), and 30 and 120 mg olezarsen Q1M for 12 doses (360 days). For each scenario, 1000 virtual subjects were generated based on the observed data from study ISIS 678354-CS3 (i.e., FCS patients).

PK/PD efficacy Assessment of Olezarsen

For Studies ISIS 678354-CS3 and ISIS 678354-CS8, reductions of TG and apoC-III from Baseline were observed at both Month 6 and 12 across all exposure tertiles. In general, relative reductions in apoC-III were similar and those in TG were more pronounced in Study ISIS 678354-CS8 compared with Study ISIS 678354-CS3.

PK/PD Safety Assessment of Olezarsen

In the analyses of Study ISIS 678354-CS3 in FCS patients, no substantial differences in safety endpoints were observed across exposure tertiles or between patients receiving olezarsen or placebo. Similar results were observed for Study ISIS 678354-CS8 in patients with HTG and ASCVD or with sHTG, with the exceptions of maximum ALT, maximum AST, and maximum decrease from Baseline platelet count. There were some differences and trends for these 3 safety parameters across exposure tertiles compared with placebo in Study ISIS 678354-CS8, but they did not appear clinically meaningful.

In the analyses of Study ISIS 678354-CS3 in FCS patients, no significant differences in safety endpoints were observed across exposure tertiles or between patients receiving olezarsen or placebo. In Study ISIS 678354-CS8 in patients with HTG and ASCVD or with sHTG, increases in ALT, AST, and

dose dependant decrease from Baseline platelet count were observed by C_{max} with similar results by $C_{through}$.

Immunogenicity

ADAs development was investigated in both healthy subjects (studies AKCEA-CS1) and patients with HTG/CVD (studies CS2 and CS8) or FCS (studies CS3, CS7 and CS13). Olezarsen shows a clear immunogenicity across all subjects included in the clinical studies. Treatment-emergent ADAs incidence rate was 33% following 60 mg Q4W for 12 weeks in healthy subjects, 32-41% following 50 or 80 mg Q4W for 52 weeks in patients with HTG/CVD, 38-45% following 50 or 80 mg Q4W for 52 weeks in patients with FCS (growing to 53-88% for a median exposure duration of 230 days in the open label study CS13) and 0-13% with placebo. Treatment-emergent ADAs were generally characterised by a late onset (29-365 days) and were persistent, with peak titers in FSC patients ranging from 50 to 25.600 ng/mL following sc 50 mg and from 50 to 51200 ng/mL following sc 80 mg olezarsen Q4W. Baseline ADA-positive rates were about 11% in healthy subjects, 19% in patients with HTG/CVD and 25-36% in patients with FCS. Immunogenicity's impact on PK, PD, efficacy and safety was investigated. While no impact on Cmax was found, 5- to 10-fold higher Ctrough levels were observed in ADA-positive FCS patients following treatment with olezarsen; such ADAs' impact on PK is correctly mentioned under SmPC 5.2 - subsection "immunogenicity. Although based on a limited number of subjects, an analysis of percent changes from baseline in fasting apoC-III or TG stratified by ADAs category in patients with FCS or HTG/CVD seemed to exclude any impact of ADAs development on olezarsen PD profile, with no neutralising activity in terms of efficacy. Furthermore, an integrated safety analysis pooling in several combinations results from studies CS2, CS3, CS7, CS8 and CS13 did not evidence any apparent correlation between treatment-related ADAs development with the frequency and severity of TEAEs or AESI. In conclusion, on the basis of the presented data, although limited in sample size, olezarsen can be considered a moderately immunogenic compound, however, ADAs development seems not to have a meaningful influence on both efficacy and safety profiles.

Dose justification

The appropriateness of a fixed dose of 80 mg once monthly delivered by prefilled syringe with autoinjector, to be used in patients with FCS was demonstrated in patients with FCS (ISIS 678354-CS3), supplemented by the efficacy and safety profile in patients with HTG and established or increased risk of ASCVD, or with sHTG (Study ISIS 678354-CS8, the Phase 1 Study ISIS 678354-CS20, the population PK and PK/pharmacodynamics modeling and simulation, and the E-R analyses). In conjunction with the population PK and PK/pharmacodynamics simulations, this supports no dose adjustments are warranted with respect to age, sex, race, geographical region, injection site, or mild to moderate hepatic or mild to moderate renal impairment.

Based on non-clinical studies higher posology could have been considered. Indeed, although results of the lipid profile in the olezarsen treated patients at Month 6 and 12 might be considered clinically relevant compared with placebo, there results are quite modest in regard with a decrease in the fasting TG and apoB-III levels demonstrated with volanesorsen. The proportion of patients who achieved TG level ≤ 880 mg/dL from baseline to Month 6 and Month 12 was small in the 80 mg olezarsen group (refer to Overall assessment of clinical efficacy).

The applicant was recommended to propose dose modifications on weight and reflect this in the SmPC if it seems to be appropriate. For the pivotal study, once monthly subcutaneously injected doses of 50 mg and 80 mg olezarsen were chosen to evaluate efficacy and safety in patients with FCS, any other dosing regimen than 80 mg QM, if needed, could be investigated as a post-approval measure and should consider both efficacy and safety.

In its response, the applicant provided a final population PK/PD model for TG that supported no trend between TG reduction and body weight. It can, thus, be concluded that the body weight does not have a substantial impact on the PD of olezarsen and that the dose should not be adjusted based on body weight.

2.5.4. Conclusions on clinical pharmacology

Overall, olezarsen's pharmacokinetic profile was well characterised. No major concerns are raised in terms of clinical pharmacology, while some minor concerns subsist in terms of BE between the Vial and the AI presentation and regarding management of patients with hepatic/renal impairment. PD profile and immunogenicity were overall well characterised. In general, the clinical pharmacology program and exposure-response and PK/PD analyses together support the proposed posology and indication.

2.5.5. Clinical efficacy

Table 7: Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
ISIS 678354-CS8	Completed Start day: 10 May 2022 End day: 20 October 2023 Enrolled: n=154 Placebo: n=39 Olezarsen 50 mg and 80 mg: n=58 and n=57, respectively Planned: n=152	A randomized, double blind, placebo controlled Phase 2b study.	Placebo Olezarsen 50 mg Olezarsen 80 mg Subcutaneous injection of olezarsen 50 or 80 mg or placebo once every 4 weeks over a 53-week Follow-up: 13 weeks - ongoing	- Males and females aged ≥ 18 years; - Clinical diagnosis of ASCVD or peripheral artery disease or at increased risk for ASCVD; - Severe hypertriglyceridemia with fasting TG ≥ 500 mg/dL (5.65 mmol/L).
ISIS 678354-CS3	Completed Start day: 11-May-2022 End day: 21-Dec-2023 Enrolled: n=66 Placebo: n=23	A randomized, double blind, placebo controlled, Phase 3 pivotal study.	Placebo Olezarsen 50 mg Olezarsen 80 mg Subcutaneous injection of olezarsen 50 or 80 mg or placebo once every 4 weeks over a	- Males and females aged ≥ 18 years; - A diagnosis of Familial Chylomicronemia Syndrome (type 1 Hyperlipoproteinemia) by documentation of confirmed homozygote,

	Olezarsen 50 mg and 80 mg: n=21 and n=22, respectively Planned: n=60		53-week treatment period Follow-up: 13 weeks (for patients not rolling over to the OLE Study ISIS 678354-CS13)	compound heterozygote or double heterozygote for loss-of-function mutations in type 1-causing genes (such as LPL, GPIHBP1, APOA5, APOC2, GPD1, or LMF1); - Fasting TG ≥ 880 mg/dL (10 mmol/L) at Screening.
ISIS 678354-CS13 No clinical efficacy data available	Ongoing Planned: n=54 Start day: 20 Dec 2021 (FPI)	An Open-Label Extension Study of ISIS 678354	Subcutaneous injection of olezarsen 80 mg (Dose reduction to 50 mg allowed if needed) Q4W over a 157-week period	Patients with FCS
ISIS 678354-CS7 (Switch) No clinical efficacy data available	Ongoing Planed: n=24 Start day: 20 Dec 2021 (FPS)	An Open-Label Safety Study of AKCEA-APOCIII-LRX[a], Administered Subcutaneously to Patients with FCS Previously Treated with Volanesorsen (ISIS 304801) Phase 3	Subcutaneous injection of olezarsen 80 mg (Dose reduction to 50 mg allowed if needed) Q4W over a 157-week period	Patients with FCS

[a] - ISIS 678354, AKCEA-APOCIII-LRX and olezarsen are the same product; FPI –first patient in; FPS – first patient screened,

2.5.5.1. Dose response study(ies)

The applicant has chosen the 80 mg and 50 mg doses of olezarsen every 4 weeks for the phase 3 study. The non-clinical consideration for this dose was based on model simulations for a population of FCS patients as obtained from the volanesorsen clinical program (non-GalNAc conjugated parent ASO of ISIS 678354).

In nonclinical studies, olezarsen demonstrated acceptable safety profiles in rodents and monkeys. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III. The NOAEL in monkeys was determined to be 6 mg/kg/wk (1680 mg/month human-equivalent dose [HED] assuming 70 kg human body weight). This NOAEL is approximately 21-fold above the proposed clinical dose (80 mg/month).

The highest olezarsen dose tested in the Phase 2 clinical study (ISIS 678354-CS2) was 50 mg once every 4 weeks, which was safe and well tolerated, and reduced TG levels by approximately 60%. Higher doses were expected to be more effective, based on the results from the ISIS 678354-CS1 Phase 1 study, which demonstrated a dose-dependent pharmacodynamic effect on the target, apoC-III, with a clear difference in the TG-lowering effect across a range of olezarsen doses from 10 mg to 120 mg (per month equivalent), compared with the placebo group. Therefore, in addition to the 50 mg dose of olezarsen, these studies also evaluated and 80 mg dose to maximize the opportunity to reduce the risk of pancreatitis.

ISIS 678354-CS1 study

The ISIS 678354-CS1 study was placebo-controlled, dose-escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of olezarsen, a GalNAc3 conjugated 2'-MOE chimeric antisense oligonucleotide targeting apoC-III, administered subcutaneously to healthy volunteers with elevated triglycerides. The study included 5 single-dose cohorts (N = 8 per cohort, total randomized 6 active: 2 placebo). The olezarsen (i.e. ISIS678354) doses were 10, 30, 60, 90, and 120 mg. The post-treatment evaluation period was Day 2 through up to Day 150 for the single dose cohorts. Subjects in the multiple-dose cohorts were evaluated at weekly dosing for 6 weeks and at every 4-week dosing 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 every 4-week dosing cohort (Cohort CC; N = 10, total randomized 6 active:4 placebo). The first multiple dose Cohort AA (≤ 20 mg) only began after at least 4 subjects in the single-dose Cohort C (≤ 80 mg) had completed dosing and Day 8 clinical and laboratory safety evaluations demonstrated an acceptable safety profile.

Table 8. Plasma Pharmacokinetic Parameters of ISIS 678354-Equivalent after single SC administration in Healthy Subjects.

Dose	n	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng*h/mL)	AUC_{0-48h} (ng*h/mL)	AUC_{last} (ng*h/mL)	CL_{last}/F (L/h)	$t_{1/2}$ (day)
10 mg	6	46.4 (21.0)	2.75 (1.00-4.02)	469 (14.8)	491 (13.4)	509 (13.3)	19.6 (13.3)	NC
30 mg	6	132 (67.4)	1.75 (1.00-8.00)	1350 (41.5)	1460 (34.7)	1630 (37.5)	18.4 (37.5)	20.4[a]
60 mg	6	284 (24.4)	1.00 (1.00-4.00)	2460 (17.9)	2780 (16.5)	3230 (21.5)	18.6 (21.5)	18.9 (36.0)
90 mg	6	1060 (81.0)	1.25 (1.00-4.00)	6270 (33.2)	6710 (30.9)	9280 (52.5)	9.69 (52.5)	39.7[a] (88.8)
120 mg	6	1160 (37.8)	2.01 (1.50-4.00)	9290 (39.4)	9610 (37.5)	11300 (41.7)	10.6 (41.7)	33.0[a] (29.0)

Abbreviations: AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-48h} = AUC from time 0 to 48 hours; AUC_{last} = AUC from time 0 to the time of last quantifiable concentration; CL_{last}/F = apparent plasma clearance from time 0 to the time of last quantifiable concentration after SC administration, calculated as SC dose divided by AUC_{last}; C_{max} = maximum plasma concentration; n = number of observations; NC = not calculated; SC = subcutaneous; $t_{1/2}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration

Data presented are geometric mean (geometric mean coefficient of variation, CV%) except T_{max}, which is presented as median (minimum-maximum).

a $t_{1/2}$ was calculated when appropriate data existed for characterization of the terminal elimination phase. The number of $t_{1/2}$ values were smaller (n=2 for 30 mg; n=5 for 90 mg; n=4 for 120 mg) compared to other parameters. The $t_{1/2}$ values could not be estimated for 10 mg due to limited detection at later time points.

The assessment of the plasma PK parameters of olezarsen showed that olezarsen was rapidly absorbed into the systemic circulation after SC administration, with the median Tmax ranging from 1 to 3 hours post-dose for all evaluated dose levels in both single- and multiple-dose groups. The Cmax and AUC increased approximately proportionally with dose in the dose range of 10 to 60 mg, and greater than dose proportionally from 60 to 120 mg, suggesting more efficient tissue uptake at lower doses. No accumulation in plasma Cmax or AUC values was observed after weekly or Q4W doses, consistent with comparable PK profiles after single and repeat doses (Table 9).

Table 9. Plasma Pharmacokinetic Parameters of ISIS 678354-Equivalent after single and multiple SC Administration in Healthy Subjects.

Dose	Study Day	n	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng*h/mL)	AUC_{0-48h} (ng*h/mL)	AUC_{0-168h} or AUC_{0-672h} (ng*h/mL)	CL_{ss}/F (L/h)	$t_{1/2}$ (day)
15 mg QW	1	6	72.3 (50.1)	2.50 (1.00-4.00)	691 (36.4)	728 (34.9)	762 (35.8)	NC	NC
	36	6	55.0 (36.5)	3.00 (1.00-6.00)	564 (43.0)	611 (42.9)	699 (41.7)	21.5 (41.7)	40.3 (109.1)
30 mg QW	1	7	128 (26.2)	1.00 (0.533-4.00)	1210 (10.0)	1290 (10.6)	1340 (11.3)	NC	NC
	36	6[a]	113 (30.8)	2.00 (1.50-3.00)	993 (17.0)	1090 (15.8)	1230 (14.9)	24.3 (14.9)	25.2 (17.0)
60 mg Q4W	1	6	418 (45.5)	1.50 (1.00-3.00)	3210 (28.0)	3310 (27.4)	3680 (26.3)	NC	29.5 (46.8)
	85	4[b]	359 (36.6)	1.50 (1.00-3.00)	3130 (23.9)	3240 (23.5)	4110 (25.8)	14.6 (25.8)	43.3[c] (9.5)

Abbreviations: AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-48h} = AUC from time 0 to 48 hours; AUC_{0-168h} = AUC from time 0 to 168 hours, reported for weekly dose groups equivalent to AUC_{0-tau} over a 7-day dosing interval; AUC_{0-672h} = AUC from time 0 to 672 hours, reported for every 4-week dose group equivalent to AUC_{0-tau} over a 28-day dosing interval; CL_{ss}/F = apparent plasma clearance at steady state after SC administration, calculated as SC dose divided by AUC_{0-168h} or AUC_{0-672h}; C_{max} = maximum plasma concentration; n = number of observations; NC = not calculated; SC = subcutaneous; $t_{1/2}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration

Data presented are geometric mean (geometric mean coefficient of variation, CV%) except T_{max}, which is presented as median (minimum-maximum).

a One subject discontinued treatment after the third dose on Day 15.

b One subject discontinued treatment after the third dose on Day 57; another subject withheld dose on Day 85 and received the fourth dose on Day 113.

c $t_{1/2}$ was calculated when appropriate data existed for characterization of the terminal elimination phase. The number of $t_{1/2}$ values was smaller (n=3 for 60 mg Q4W on Day 85) compared to other parameters.

Pharmacodynamic results showed dose-dependent and statistically significant sustained reductions from baseline in fasting plasma apoC-III and TG levels, with particularly marked reductions across all single-dose and multiple-dose cohorts. In the monthly multiple-dose cohort (60 mg), reductions of 61% and 65% (TG) and 80% and 83% (apoC-III) were seen at Day 43 and Day 92 (one week after the last dose), respectively. The effects were sustained at Day 113 with reductions of 79% (apoC-III) and 58% (TG). Also, reductions in apoB of 22% and 30% and increases in HDL-C of 64% to 76% were observed at Day 43 and Day 92, respectively, in the 60 mg monthly multiple-dose group.

ISIS 678354-CS2 study

The ISIS 678354-CS2 study was a randomized, rouble-blind, placebo-controlled, dose-ranging phase 2 study of olezarsen administered subcutaneously to patients with hypertriglyceridemia and established cardiovascular disease (CVD) or at high risk for CVD. The study included a screening, a treatment period (52 weeks), and a follow-up period (13 weeks). Patients were randomized in the 4 parallel-dose cohorts (Cohorts A, B, C or D). Within each cohort, patients were randomized in a 4:1 ratio to receive olezarsen or matching volume of placebo. Study Drug (olezarsen or placebo) was administered by subcutaneous (SC) injection every week (QW), every 2 weeks (Q2W), or every 4 weeks (Q4W), depending on cohort assignment, for up to 52 weekly doses, up to 26 every 2-week doses, or up to 13

every 4-week doses. The study was aimed to evaluate the safety and efficacy of olezarsen in a 5-fold range of drug exposure utilizing 3 different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. The proposed range of doses were expected to provide sufficient data to characterize the dose- and exposure-response relationship.

Four dosing regimens were thought to be provided total monthly drug exposures equivalent to 10, 30, 40, and 50 mg administered as 10 mg Q4W, 15 mg Q2W, 10 mg every week, and 50 mg Q4W, respectively. These doses were predicted to provide reductions from Baseline in serum TG ranging from approximately 30% to 64% at the end of the dosing interval at steady- state based on a preliminary PK/PD model developed using the available Phase 1 data.

Table 10. Study Drug Dosing Information.

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 678354
A	10 mg ISIS 678354 or placebo (Every 4 weeks)	0.10 mL	≤ 13	≤ 130 mg
B	50 mg ISIS 678354 or placebo (Every 4 weeks)	0.50 mL	≤ 13	≤ 650 mg
C	15 mg ISIS 678354 or placebo (Every 2 weeks)	0.15 mL	≤ 26	≤ 390 mg
D	10 mg ISIS 678354 or placebo (Every week)	0.10 mL	≤ 52	≤ 520 mg

Treatment with olezarsen within range of doses studied (10 mg to 50 mg Q4W) was safe and well tolerated. The statistically significant reductions from baseline to the PAT at Week 25 or Week 27, depending on cohort assignment, were observed for TG and apoC-III levels (by 62% and 74%, respectively for the highest 50 mg Q4W group), as well as for other atherogenic lipids/lipoproteins: VLDL-C, remnant cholesterol, non-HDL-C, and apo-B). Importantly, proportions of patients reaching normal TG levels < 150 mg/dL have increased dose-dependently, and 91% of patients treated with 50 mg Q4W have reached these normal TG levels.

To justify selection of the 80 mg dose and to bridge between the once-every-4-weeks dosing regimen used in the clinical program to the once-monthly regimen proposed for commercialization, simulations were performed using the final population PK and PK/pharmacodynamics models and applying the covariate distribution from Study ISIS 678354 CS3 in patients with FCS.

The simulated olezarsen PK and pharmacodynamics profiles following the administration of olezarsen 80 mg once every 4 weeks 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. The comparison of the once-every-4-weeks with the once-monthly dosing regimen showed no meaningful differences in the simulated PK exposure (Cmax,ss, Ctrough,ss, and AUCtau,ss). Similarly, apoC-III or TG profiles between once-every-4-weeks and once-monthly dosing were nearly identical (< 1.5% difference at steady-state).

2.5.5.2. Main study(ies)

ISIS 678354-CS3

Methods

The study ISIS 678354-CS3 was a pivotal, randomized, double-blind, placebo-controlled, phase 3 trial administered subcutaneously in patients with Familial Chylomicronemia Syndrome (FCS) to evaluate efficacy and safety of subcutaneously administered olezarsen (AKCEA-APOCIII-LRX). The efficacy

evaluation was based on measuring the changes in lipid and apolipoprotein parameters (i.e., TG, apoC-III, apoB-48, and non-HDL-C), the incidence rate of acute pancreatitis (adjudicated by a blinded, independent committee according to the Atlanta Classification of acute pancreatitis and as outlined in the Pancreatitis Adjudication Charter), and changes in broader healthcare and patient-reported outcomes.

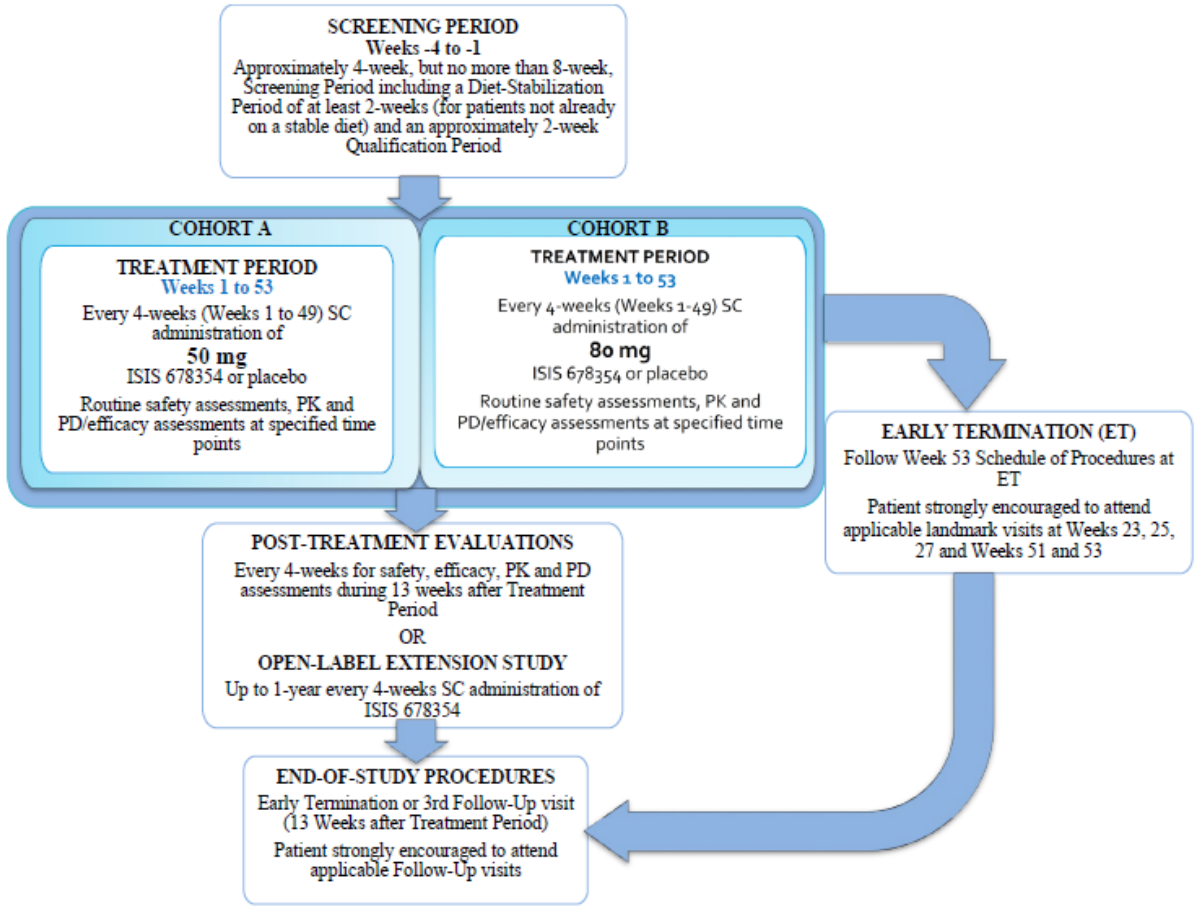


Figure 6: Study ISIS 678354-CS3 schema

- **Study Participants**

The recruitment of patients was done at 29 sites including 9 sites in the United States (US), 3 sites in Canada, 16 sites in the European Union (EU) countries, and 1 site in the United Kingdom (UK). Patients were eligible to participate in this study based on the inclusion and exclusion criteria.

Key inclusion criteria:

- Signed and dated written informed consent and any authorizations required by local law and were able to comply with all study requirements.
- Aged ≥ 18 years at the time of informed consent.
- 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, GPIHBP1, APOA5, APOC2, GPD1, or LMF1).
- Fasting TG ≥ 880 mg/dL (10 mmol/L) at Screening. If the fasting TG was < 880 mg/dL, up to 2 additional tests may have been performed, with any single test used to qualify.

- History of pancreatitis (defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made) within 10 years prior to Screening. Patients without a recorded history of pancreatitis, or no recorded history within 10 years prior to Screening, were also eligible but their enrollment was capped at 35% (i.e., ≤ 21) of the 60 planned patients.
- Willing to follow a diet comprising ≤ 20 g fat per day during the study.
- Willing to complete all Patient Reported Outcome (PRO) assessments throughout the study, as described in (see Study Protocol Section 6.2.5).
- The following concomitant medications were 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 was allowed at Investigator's discretion):

    a. Statins, omega-3 fatty acids (prescription and OTC), fibrates, or other lipid-lowering medications. Patients taking OTC omega-3 fatty acids were to have made every effort to remain on the same brand through the end of the study

    b. Antidiabetic medications

Patients also were allowed to use antihypertensive medications, oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) and tamoxifen, oestrogens or progestins. For a full list of inclusion criteria please refer to the submitted CSR of the study ISIS 678354-CS3.

Key exclusion criteria:

- 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.
- Active pancreatitis within 4 weeks prior to Screening
- Screening laboratory results as follows, or any other clinically significant abnormalities in screening
- laboratory values that would have rendered a patient unsuitable for inclusion:

    a. Platelet count < 100,000/mm3 at Screening or Qualification. If the platelet count was < 100,000/mm3, up to 2 additional tests may have been performed to qualify at both Screening and Qualification.

    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3.0 × upper limit of normal (ULN).

    c. Total bilirubin > ULN unless due to Gilbert's syndrome.

    d. Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m2 (as determined by the Chronic Kidney Disease Epidemiology [CKD-EPI] formula for creatinine clearance).

    e. Urine protein/creatinine ratio (UPCR) ≥ 500 mg/g, or urine albumin/creatinine (UACR) ratio ≥ 300 mg/g.

- 4. Uncontrolled arterial hypertension (blood pressure [BP] > 160/100 mm Hg)
- 5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening.

- Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C.
- Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening, or 5 half-lives, whichever was longer. This exclusion did not apply to vaccines.
- Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening, or 5 half-lives, whichever was longer. This exclusion did not apply to vaccines.

For a full list of exclusion criteria please refer to the submitted CSR of the study ISIS 678354-CS3.

- **Treatments**

As per study protocol, patients were assigned to the treatment with olezarsen or placebo, which were administered subcutaneously (SC) by Study Center staff as follows:

• Cohort A: Patients were randomly assigned 2:1 to receive 50 mg olezarsen (0.5 mL) or matching volume of placebo SC once every 4 weeks for Weeks 1 to 49.

• Cohort B: Patients were randomly assigned 2:1 to receive 80 mg olezarsen (0.8 mL) or matching volume of placebo SC once every 4 weeks for Weeks 1 to 49.

Initial selection and timing of study drug (olezarsen or placebo) doses for each patient were made based on the cohort and drug product assigned through randomization (Clinical Study Report, Section 9.4.3). For each individual patient in the 50 mg cohort (Cohort A), Study Drug was intended to be administered SC as a single 0.5 mL injection once every 4 weeks for Weeks 1-49 for a total of 13 doses. For each individual patient in the 80 mg cohort (Cohort B), Study Drug was intended to be administered SC as a single 0.8 mL injection once every 4 weeks for Weeks 1-49 for a total of 13 doses. Self-administration was allowed after appropriate training of patient and/or caregiver.

With respect to changes in dose and/or schedule of drug product, the safety monitoring rules (i.e. liver chemistry tests, renal function and platelet count results, stopping rules, and criteria for re-dosing after interruption of treatment for this study are provided in the Study Protocol Section 8.5 and Section 8.6 (Appendix 16.1.1). Other adjustments, including dose interruptions, and/or decreasing the dose were allowed for safety or tolerability after consultation with the Sponsor Medical Monitor. Dose adjustments were not to occur unless absolutely necessary prior to the primary analysis time point (Month 6).

- **Objectives**

The primary objective of this study was to evaluate the efficacy of olezarsen as compared to placebo on the percent change in fasting triglycerides (TG) from Baseline.

The secondary objectives were to evaluate the efficacy of olezarsen as compared to placebo on the following:

• Percent change in fasting apolipoprotein C-III (apoC-III) from Baseline

· Proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline

• Percent change in fasting apolipoprotein B-48 (apoB-48) from Baseline

• Percent change in fasting non-high-density-lipoprotein cholesterol (non-HDL-C) from Baseline

• Adjudicated acute pancreatitis event rate in patients with a prior history of pancreatitis within 10 years prior to Screening

• Adjudicated acute pancreatitis event rate

· Proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline

· Proportion of patients who achieve fasting TG ≤ 880 mg/dL (10 mmol/L)

· Adjudicated acute pancreatitis event rate in patients with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment

· Proportion of patients who achieve fasting TG ≤ 500 mg/dL (5.7 mmol/L)

- **Outcomes/endpoints**

The primary endpoint was the mean percent change in fasting TG from Baseline at the primary analysis time point compared with placebo. The primary analysis time point was at Month 6 and was defined as the average of Weeks 23, 25, and 27.

Secondary efficacy endpoints, in order of hierarchy by priority for analysis, included the following:

• 1: comparison of percent change in fasting TG from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set

• 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 Full Analysis Set

• 3: comparison of percent change in fasting apoC-III from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set

· 4: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in Full Analysis Set

• 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 Full Analysis Set

• 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 Full Analysis Set

• 7: comparison of percent change in fasting TG from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set

• 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 Full Analysis Set

• 9: comparison of percent change in fasting apoC-III from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set

· 10: comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in Full Analysis Set

• 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 Full Analysis Set

• 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 Full Analysis Set

• 13: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with a prior history of pancreatitis within 10 years prior to Screening

• 14: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in Full Analysis Set

• 15: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with a prior history of pancreatitis within 10 years prior to Screening

• 16: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the Full Analysis Set

· 17: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between olezarsen 80 mg group and pooled placebo in Full Analysis Set

• 18: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set

• 19: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set

· 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 Full Analysis Set

· 21: comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to the primary analysis time point between olezarsen 50 mg group and pooled placebo in Full Analysis Set

• 22: comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set

• 23: comparison of percent change in fasting apoB-48 from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set

· 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 Full Analysis Set

• 25: comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment

• 26: comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment

· 27: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between olezarsen 80 mg group and pooled placebo in Full Analysis Set

· 28: comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the primary analysis time point between olezarsen 50 mg group and pooled placebo in Full Analysis Set

Additional/exploratory endpoints included frequency and percentage of patient-reported abdominal pain and other FCS-related symptoms, diet, and impacts, HRQoL, cognitive function, and ER visits, incidence of all-cause hospitalizations and total inpatient days, compared with placebo (post analysis note: the exploratory analyses in the Statistical Analysis section below defines the full name of tests).

- **Sample size**

Based upon prior clinical trial experience with FCS patients, the SD of the percent change from Baseline in TGs was approximately 46%. With 14 patients in each ISIS 678354 treatment group and

14 in the pooled placebo group, there would be a 90% power to detect a 60% difference between each ISIS 678354 treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the ISIS 678354 treatment patients and no change in the placebo patients. Approximately 60 patients were planned to be enrolled in this trial to account for potential early dropouts and to facilitate some general safety evaluations. Eligible patients were randomized 1:1 to Cohort A or Cohort B and each cohort further randomized 2:1 (ISIS 678354:placebo) and stratified for:

- Prior history of pancreatitis within 10 years prior to Screening* vs. no history of pancreatitis or no history within 10 years prior to Screening (*History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made)
- Previous treatment with volanesorsen

- **Randomisation and Blinding (masking)**

This was a double-blind study. The Sponsor, Investigator, and patients were blinded to post-Baseline laboratory lipid and apolipoprotein panel results (TG, apoC-III, total cholesterol, LDL cholesterol, HDL cholesterol, apoB, apoB-48, chylomicron-TG, VLDL, non-HDL-C, and apoA-1) throughout the study until all patients had completed the study and the database had been locked. Beginning at Week 27, if any patient had an LDL-C > 130 mg/dL (> 100 mg/dL for patients with T2DM or CAD with Baseline LDL-C > 100 mg/dL) on 2 consecutive visits, the LDL-C values for this patient were to be unblinded for the remainder of the study.

Using an Interactive Response Technology (IRT) system, eligible patients were randomly assigned 1:1 to Cohort A or Cohort B and each cohort further randomly assigned 2:1 to receive olezarsen or placebo. Patients were stratified for the following:

- Prior history of pancreatitis within 10 years prior to Screening versus no history of pancreatitis or no history within 10 years prior to Screening (NOTE: History of pancreatitis was defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made).
- Previous treatment with volanesorsen (Yes vs. No).

- **Statistical methods**

Study ISIS 678354 CS8

All primary analyses were conducted using the Full Analysis Set and Per Protocol Set populations; the former population was the basis for the primary efficacy analysis. The percent change from Baseline at Month 6 in fasting TG between each olezarsen treatment group (olezarsen 50 mg or olezarsen 80 mg) compared with a pooled placebo group, and percent changes in other primary sensitivity efficacy endpoints, as of the data cutoff date, from Baseline at Month 6 were summarized. Estimates of least squares means of percent change from Baseline in fasting TG for each treatment group, as well as the treatment differences relative to the placebo group and the corresponding standard error, were provided; these estimates were combined to provide an overall estimate with corresponding CIs and p values. The primary efficacy endpoint was the percent change in fasting TG from Baseline at the primary analysis time point compared with the placebo group. The primary analysis time point was Month 6, which was defined as the average of Week 25 and Week 27.

The primary and secondary efficacy endpoint analyses were conducted using a sequential hierarchical ranking strategy. For primary endpoint analyses, the 2 treatment arms were to be compared against the placebo group using the following hierarchical testing procedure: the olezarsen 80 mg group was to be compared with the placebo group at the 2-sided alpha level of 0.05; if the comparison was

statistically significant (p-value < 0.05), then the olezarsen 50 mg group was to be compared with the placebo group at the alpha level of 0.05. If the comparison of the olezarsen 80 mg group to the placebo group was not statistically significant, then the comparison of the olezarsen 50 mg group to placebo, and all secondary endpoints, were to be considered exploratory.

The primary analysis of the primary endpoint was to compare the percent change from Baseline to Month 6 in fasting TG between each olezarsen treatment group vs. placebo group using the FAS. If patients had intercurrent event(s) before Week 25, e.g., treatment discontinuation, use of additional medication, changes in background or concomitant treatments, the Treatment Policy strategy was implemented, the patients' assessments post intercurrent events were continued to be collected. All assessments including those post the intercurrent events were utilized in the analysis. The sensitivity analyses were also conducted for the primary endpoint: the primary efficacy analysis with ANCOVA model was repeated in the PPS and in the Completer Set (Subset of FAS), robustness exploration was performed in FAS, tipping point analysis (FAS), and ANCOVA model using log-transformed data (FAS) were also conducted.

Full Analysis Set (FAS) consisted of all patients who were randomly assigned and received any amount of study drug (olezarsen or placebo) as of the data cutoff date (15 Sep 2023). The Full Analysis Set represented the practically feasible intent-to-treat population as delineated in the International Council for Harmonisation Guideline E9.

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

There was no interim analysis planned for the study. The multiplicity was controlled by using a hierarchical ranking strategy in the following testing sequence. All tests will be conducted at a two-sided alpha level of 0.05. For the primary endpoint family, the 2 treatment arms will be compared against placebo using the hierarchical testing procedure, in which the olezarsen 80 mg treatment group will be compared to the placebo at the 2-sided alpha level of 0.05, if the comparison is statistically significant (p < 0.05), then the olezarsen 50 mg treatment group is compared against the placebo at the alpha level of 0.05.

Results

- **Participant flow**

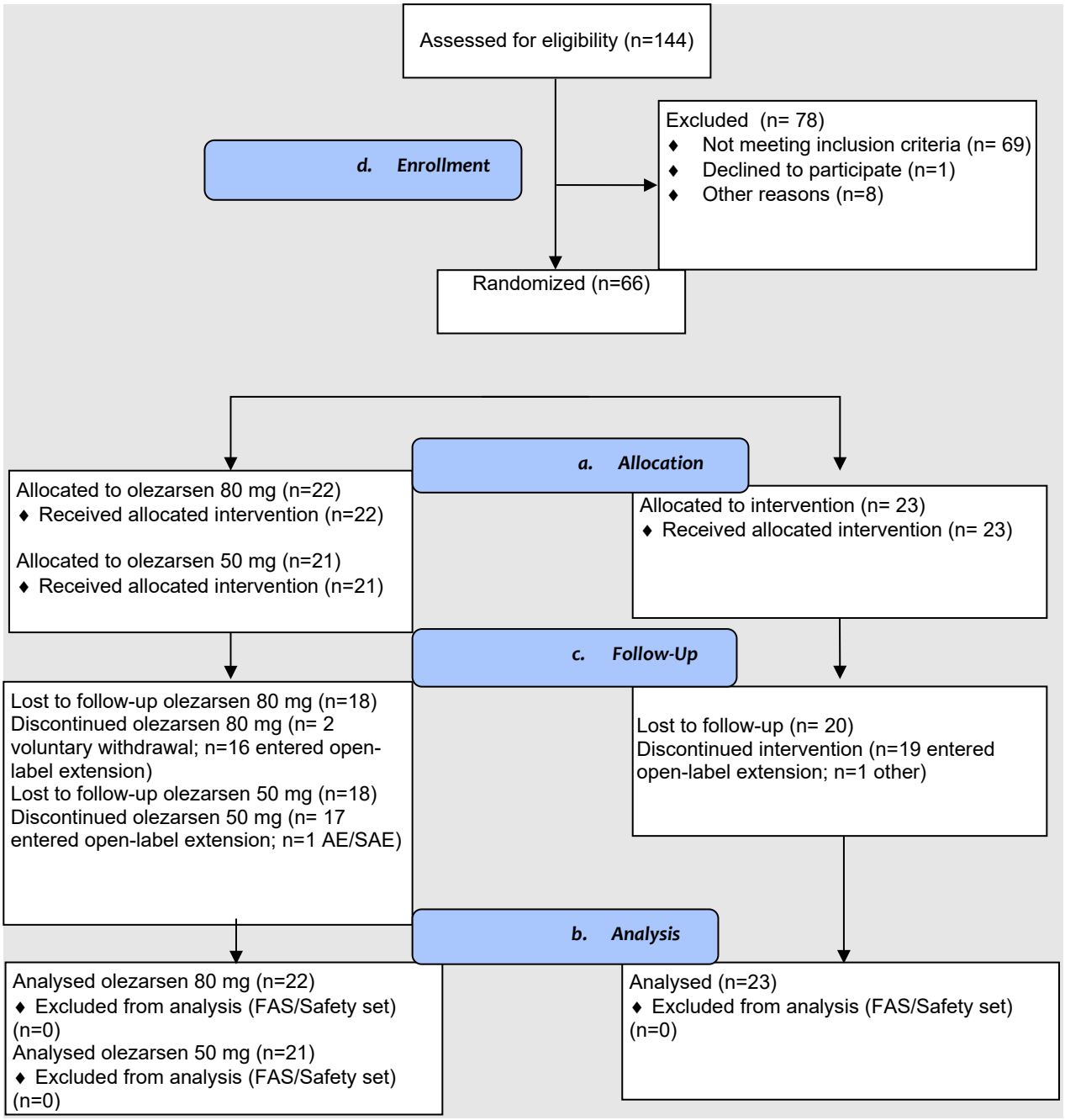


Figure 7: Participant flow

- **Recruitment**

First Patient Screened: 18 Nov 2020

First Patient Dosed: 17 Dec 2020

Last Patient Enrolled: 11 Jul 2022

Last Patient, Last Dose: 20 Jun 2023

Last Patient, Last Visit: Patients still in follow-up at time of data cutoff

Data Cutoff: 14 Jul 2023 (End of Treatment)

Database Lock Date: 30 Aug 2023

- **Conduct of the study**

Please refer to Statistical methods.

- **Baseline data**

Table 11. Summary of Patient Demographics and Baseline Characteristics (Full Analysis Set)

Demographic/Baseline Characteristics (Statistic)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Age at Informed Consent (years)			
Mean (SD)	44.0 (14.67)	43.2 (12.11)	47.7 (13.30)
Minimum, Maximum	21, 69	18, 74	25, 78
Age Category (years), n (%)			
< 65	20 (87.0)	20 (95.2)	20 (90.9)
≥ 65	3 (13.0)	1 (4.8)	2 (9.1)
Sex, n (%)			
Female	12 (52.2)	15 (71.4)	11 (50.0)
Male	11 (47.8)	6 (28.6)	11 (50.0)
If female, n (%)			

Table 12. Summary of Patient Demographics and Baseline Characteristics (Full Analysis Set) (continued)

Demographic/Baseline Characteristics (Statistic)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Post-menopausal	4 (33.3)	3 (20.0)	4 (36.4)
Surgically sterile	3 (25.0)	3 (20.0)	5 (45.5)
Ethnicity, n (%)			
Hispanic or Latino	3 (13.0)	3 (14.3)	1 (4.5)
Not Hispanic or Latino	20 (87.0)	18 (85.7)	21 (95.5)
Race, n (%)			
White	22 (95.7)	17 (81.0)	17 (77.3)
Asian	0	3 (14.3)	3 (13.6)
Native Hawaiian or Other Pacific Islander	0	1 (4.8)	0
Other	1 (4.3)	0	2 (9.1)
Region, n (%)			
North America (including the US)	12 (52.2)	9 (42.9)	8 (36.4)
Europe (including United Kingdom)	11 (47.8)	12 (57.1)	14 (63.6)
Country, n (%)			
Canada	5 (21.7)	4 (19.0)	1 (4.5)
France	1 (4.3)	0	2 (9.1)
Italy	3 (13.0)	0	3 (13.6)
Netherlands	1 (4.3)	3 (14.3)	2 (9.1)
Norway	0	0	1 (4.5)
Portugal	1 (4.3)	1 (4.8)	1 (4.5)
Slovakia	1 (4.3)	0	2 (9.1)
Spain	3 (13.0)	5 (23.8)	2 (9.1)
Sweden	1 (4.3)	2 (9.5)	0
United Kingdom	0	1 (4.8)	1 (4.5)
United States	7 (30.4)	5 (23.8)	7 (31.8)
Body Weight (kg)			
Mean (SD)	67.827 (16.0854)	61.166 (11.5773)	68.447 (16.6512)
Minimum, Maximum	44.00, 101.90	45.00, 89.30	35.80, 112.70
BMI (kg/m^2)			
Mean (SD)	24.20 (4.121)	22.43 (3.459)	25.10 (5.977)
Minimum, Maximum	16.9, 31.5	17.1, 30.2	14.9, 46.5
Diabetic status, n (%)			
No	17 (73.9)	18 (85.7)	15 (68.2)
Type I or Type II	6 (26.1)	3 (14.3)	7 (31.8)
Genetic test outcome, n (%)			
Genetic confirmation of loss-of-function mutations [a]	23 (100)	21 (100)	22 (100)
LPL			
Homozygote	16 (69.6)	14 (66.7)	10 (45.5)
Hemizygote	0	0	1 (4.5)
Compound heterozygote	5 (21.7)	3 (14.3)	5 (22.7)
Double heterozygote	0	0	1 (4.5)

Table 13. Summary of Patient Demographics and Baseline Characteristics (Full Analysis Set) (continued)

Demographic/Baseline Characteristics (Statistic)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
APOA5			
Homozygote	1 (4.3)	0	1 (4.5)
Double heterozygote	0	0	1 (4.5)
GPIHBP1			
Homozygote	1 (4.3)	2 (9.5)	1 (4.5)
LMF1			
Homozygote	0	1 (4.8)	0
Compound heterozygote	0	0	1 (4.5)
APOC2			
Homozygote	0	1 (4.8)	2 (9.1)

Note: Percentages were based on the number of Full Analysis Set patients in each treatment group or overall.
Note: Baseline for body weight and BMI was defined as the last non missing assessment prior to the first dose of olezarsen or placebo.
[a] Genetic confirmation occurred either as a positive test outcome from the central genetics laboratory or, if the test outcome by the central genetics laboratory was indeterminate, a subject matter expert assessed that the results were consistent with FCS.
Abbreviations: APOA5 = apolipoprotein A-5; APOC2 = apolipoprotein C2; BMI = body mass index; FCS = familial chylomicronemia syndrome; GPIHBP1 = glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1; LMF1 = lipase maturation factor 1; LPL = lipoprotein lipase; P75 = 75th percentile; P25 = 25th percentile; SD = standard deviation; US = United States.

Mean BMI at Baseline were similar across the treatment groups. The proportion of patients with diabetes at enrolment was higher in the olezarsen 80 mg group (31.8%) compared with the olezarsen 50 mg group (14.3%) and the placebo group (26.1%) (Table 13, see above).

Table 14 Summary of Baseline Lipid and Lipoprotein Panel (Full Analysis Set)

Baseline Lipid/Lipoprotein Parameter (Statistic)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Fasting Triglycerides (mg/dL)			
Mean (SD)	2595.7 (1255.72)	2683.8 (1235.06)	2613.1 (1498.96)
Median (min, max)	2493.0 (334, 5436)	2678.5 (779, 5965)	2086.0 (683, 6898)
Fasting apoC-III (mg/dL)			
Mean (SD)	27.681 (11.7115)	27.734 (10.4919)	27.542 (11.5699)
Median (min, max)	25.550 (9.02, 55.26)	27.770 (11.49, 50.60)	28.425 (9.94, 48.97)
Fasting Total Cholesterol (mg/dL)			
Mean (SD)	285.96 (113.928)	323.36 (100.539)	277.39 (99.272)
Median (min, max)	266.00 (45.5, 507.5)	341.00 (184.5, 469.5)	263.75 (93.5, 545.0)
Fasting LDL Cholesterol - Ultracentrifugation (mg/dL)			
Mean (SD)	16.7 (8.40)	17.6 (8.52)	22.8 (14.11)
Median (min, max)	13.0 (4, 38)	16.0 (7, 46)	21.0 (3, 56)
Fasting HDL Cholesterol (mg/dL)			
Mean (SD)	14.7 (3.77)	15.7 (4.01)	14.5 (4.45)
Median (min, max)	14.5 (8, 27)	16.0 (8, 24)	15.3 (5, 23)
Fasting apoB (mg/dL)			
Mean (SD)	59.748 (18.9466)	65.179 (13.4848)	58.441 (17.2289)
Median (min, max)	53.000 (32.80, 117.00)	65.200 (34.30, 96.75)	57.950 (32.30, 85.20)
Fasting apoB-48 (mg/dL)			
Mean (SD)	14.194 (14.1980)	18.545 (15.2622)	11.648 (8.1112)
Median (min, max)	8.395 (1.20, 60.87)	12.745 (3.58, 60.33)	8.750 (1.76, 28.60)
Fasting Chylomicron-TG (mg/dL)			
Mean (SD)	2268.7 (1236.99)	2302.3(1265.32)	2477.0 (2123.40)
Median (min, max)	1958.0 (227, 4852)	2066.5 (449, 5696)	1872.5 (375, 9867)
Fasting Chylomicron-C + VLDL-C (mg/dL)[a]			
Mean (SD)	255.3 (114.37)	293.2 (103.31)	245.7 (110.90)
Median (min, max)	244.0 (30, 490)	314.0 (122, 451)	222.8 (63, 572)
Fasting Non-HDL-C (mg/dL)			
Mean (SD)	271.3 (113.31)	307.6 (101.75)	262.9 (100.36)
Median (min, max)	251.0 (38, 494)	327.0 (167, 458)	247.0 (77, 540)
Fasting apoA-1 (mg/dL)			
Mean (SD)	104.8 (19.35)	107.8 (19.34)	99.4 (19.15)
Median (min, max)	103.5 (54, 164)	105.5 (75, 147)	98.0 (54, 149)

Note: Percentages were based on the number of Full Analysis Set patients in each treatment group or overall.
Note: Baseline for lipid measurements was defined as the average of the pre-dose measurement on Day 1 and the last measurement closest to Day 1 (last measurements from Qualification Period and Screening Period), prior to administration of the first dose of olezarsen or placebo. If 1 of the 2 measurements was missing, the other measurement was assigned as the Baseline value. Only measurements taken in a fasting state were considered in the Baseline determination.
[a]Defined in the protocol as VLDL-C, the assessing laboratory inadvertently processed the samples to determine this variable as the cholesterol content in the density fraction < 1.006 g/mL, which represents the combined cholesterol content of the chylomicron and VLDL fractions.
Abbreviations: apoA-1 = apolipoprotein A-1; apoB = apolipoprotein B; apoB-48 = apolipoprotein B-48; apoC-III = apolipoprotein C-III; HDL = high-density lipoprotein; LDL = low-density lipoprotein; max = maximum; min = minimum; non-HDL-C = non-high-density-lipoprotein cholesterol; SD = standard deviation; TG = triglycerides; VLDL-C = very-low-density-lipoprotein cholesterol.

Targeted cardiac and pancreatitis medical histories were generally consistent with the disease severity of enrolled patients across treatment groups. History of pancreatitis was defined as a recorded

diagnosis of acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made (Clinical Study Report, section 9.7.2).

Table *15*. Targeted Medical History (Safety Set)

Category of History Number of Patients/Episodes (Statistics)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Cardiac-Related History			
Patients with CAD, n (%)	1 (4.3)	0	1 (4.5)
Patients with Acute MI, n (%)	0	0	1 (4.5)
Patients with PCI, n (%)	0	0	1 (4.5)
Patients with CABG, n (%)	0	0	0
Patients with Unstable Angina, n (%)	0	0	0
Patients with Heart Failure, n (%)	0	0	0
Patients with Hospitalization for Heart Failure (in the past), n (%)	0	0	0
Patients with Urgent Outpatient visit for Heart Failure (in the past), n (%)	0	0	0
Patients with Stroke (CVA/TIA), n (%)	1 (4.3)	0	0
Patients with Peripheral Revascularization, n (%)	0	0	0
Pancreatitis History			
Patients with a history of acute pancreatitis or severe abdominal pain episode or other symptoms suggestive of pancreatitis with hospitalization, n (%)	19 (82.6)	19 (90.5)	15 (68.2)
Number of Episodes Last 10 Years			
Mean (SD, SEM)	6.3 (16.29, 3.40)	3.4 (3.98, 0.87)	3.4 (6.01, 1.28)
Median (P25, P75)	2.0 (0.0, 5.0)	2.0 (0.0, 6.0)	1.0 (0.0, 3.0)
Min, Max	0, 78	0, 14	0, 25
Number of Episodes Last 5 Years			
Mean (SD, SEM)	3.6 (8.24, 1.72)	1.8 (2.10, 0.46)	1.5 (3.16, 0.67)
Median (P25, P75)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)
Min, Max	0, 38	0, 8	0, 15
Patients with Acute pancreatitis or severe abdominal pain episode or other symptoms suggestive of pancreatitis without hospitalization (but with ER or Urgent Care visit), n (%)	9 (39.1)	7 (33.3)	6 (27.3)
Number of Episodes Last 10 Years			
Mean (SD, SEM)	0.3 (0.88, 0.18)	0.7 (2.22, 0.48)	1.5 (5.16, 1.10)
Median (P25, P75)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Min, Max	0, 4	0, 10	0, 24
Number of Episodes Last 5 Years			
Mean (SD, SEM)	0.2 (0.52, 0.11)	0.1 (0.36, 0.08)	0.2 (0.50, 0.11)

Category of History Number of Patients/Episodes (Statistics)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Median (P25, P75)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Min, Max	0, 2	0, 1	0, 2
Documented Diagnosis of Acute Pancreatitis or Severe Abdominal Pain Episode or Other Symptoms Suggestive of Pancreatitis with Hospitalisation or without Hospitalisation, n (%)	21 (91.3)	20 (95.2)	18 (81.8)
Number of Episodes Last 10 Years			
Mean (SD, SEM)	6.6 (16.48, 3.44)	4.1 (4.36, 0.95)	4.8 (7.49, 1.60)
Median (P25, P75)	3.0 (0.0, 5.0)	3.0 (0.0, 7.0)	1.5 (1.0, 5.0)
Min, Max	0, 79	0, 14	0, 25
0	6 (26.1)	5 (23.8)	1 (4.5)
> 0 to 5	10 (43.5)	7 (33.3)	13 (59.1)
> 5 to 10	3 (13.0)	5 (23.8)	1 (4.5)
> 10 to 15	0	3 (14.3)	0
> 15 to 20	0	0	1 (4.5)
> 20 to 40	1 (4.3)	0	2 (9.1)
> 40	1 (4.3)	0	0
Number of Episodes Last 5 Years			
Mean (SD, SEM)	3.8 (8.40, 1.75)	1.9 (2.30, 0.50)	1.7 (3.17, 0.67)
Median (P25, P75)	1.0 (0.0, 4.0)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)
Min, Max	0, 39	0, 9	0, 15
0	7 (30.4)	6 (28.6)	3 (13.6)
> 0 to 5	12 (52.2)	13 (61.9)	14 (63.6)
> 5 to 10	0	1 (4.8)	0
> 10 to 15	0	0	1 (4.5)
> 15 to 20	1 (4.3)	0	0
> 20 to 40	1 (4.3)	0	0
> 40	0	0	0
Patients with Active pancreatitis within 4 weeks prior to Informed Consent, n (%)	0	0	0
Patients with Known Chronic Pancreatitis, n (%)	6 (26.1)	3 (14.3)	8 (36.4)

Note: Percentages were based on the number of safety patients in each treatment group or overall.
Note: Number of Episodes Last 10 (5) Years considered as 0 for patients who answered "No".
Abbreviations: CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CVA = cerebrovascular accident; ER = emergency room; MI = myocardial infarction; min = minimum;

Overall, prior, concomitant, and background medication use was similar across the treatment groups. The lipid-lowering background medications background medications and antidiabetic drugs before the first dose of study treatment and continued after first study drug are provided in the Table 16 below.

Table 16. Lipid-lowering background medications and antidiabetic drugs before the first dose of study treatment and continued after first study drug.

Medication Category Preferred Term	Placebo (N=23) n (%)	Olezarsen 50 mg (N=21) n (%)	Olezarsen 80 mg (N=22) n (%)	Total Olezarsen (N=43) n (%)	Overall (N=66) n (%)
Number of patients with at least one background medication	23 (100)	20 (95.2)	20 (90.9)	40 (93.0)	63 (95.5)
Statin	7 (30.4)	4 (19.0)	5 (22.7)	9 (20.9)	16 (24.2)
ATORVASTATIN	3 (13.0)	1 (4.8)	2 (9.1)	3 (7.0)	6 (9.1)
ROSUVASTATIN	2 (8.7)	3 (14.3)	1 (4.5)	4 (9.3)	6 (9.1)
ROSUVASTATIN CALCIUM	2 (8.7)	0	1 (4.5)	1 (2.3)	3 (4.5)
PITAVASTATIN CALCIUM	0	0	1 (4.5)	1 (2.3)	1 (1.5)
PRAVASTATIN	0	0	1 (4.5)	1 (2.3)	1 (1.5)
Omega-3 fatty acid	7 (30.4)	6 (28.6)	12 (54.5)	18 (41.9)	25 (37.9)
FISH OIL	6 (26.1)	1 (4.8)	6 (27.3)	7 (16.3)	13 (19.7)
OMEGA-3-ACID ETHYL ESTER	0	4 (19.0)	2 (9.1)	6 (14.0)	6 (9.1)
EICOSAPENTAENOIC ACID ETHYL ESTER	1 (4.3)	1 (4.8)	3 (13.6)	4 (9.3)	5 (7.6)
DOCOSAHEXAENOIC ACID ETHYL ESTER;EICOSAPENTAENOIC ACID ETHYL ESTER	0	0	1 (4.5)	1 (2.3)	1 (1.5)
Fibrate	11 (47.8)	8 (38.1)	11 (50.0)	19 (44.2)	30 (45.5)
FENOFIBRATE	8 (34.8)	5 (23.8)	7 (31.8)	12 (27.9)	20 (30.3)
GEMFIBROZIL	3 (13.0)	2 (9.5)	4 (18.2)	6 (14.0)	9 (13.6)
BEZAFIBRATE	0	1 (4.8)	0	1 (2.3)	1 (1.5)

Note 1: Background Medications were defined as any medications that patients were exposed to before first dose and continued after first dose of study drug.
Note 2: A patient was counted once for each medication category and preferred term even if multiple medications were reported by the patient.
Note 3: Percentages were based on the number of safety patients in each treatment group or overall.
Note 4: Background Medications were classified according to WHO-DDE version GLOBAL B3 MAR 2023.

Source Data: ADCM
Program name: t_adcm_background.sas Run date: 23JAN2024 02:21 Database last modified: 30AUG2023

Medication Category Preferred Term	Placebo (N=23) n (%)	Olezarsen 50 mg (N=21) n (%)	Olezarsen 80 mg (N=22) n (%)	Total Olezarsen (N=43) n (%)	Overall (N=66) n (%)
Other lipid-lowering (Excluding Omega-3 fatty acid)	3 (13.0)	0	3 (13.6)	3 (7.0)	6 (9.1)
EZETIMIBE	3 (13.0)	0	2 (9.1)	2 (4.7)	5 (7.6)
EVOLOCUMAB	0	0	1 (4.5)	1 (2.3)	1 (1.5)
Antidiabetic	6 (26.1)	3 (14.3)	8 (36.4)	11 (25.6)	17 (25.8)
METFORMIN	5 (21.7)	0	5 (22.7)	5 (11.6)	10 (15.2)
INSULIN GLARGINE	3 (13.0)	2 (9.5)	1 (4.5)	3 (7.0)	6 (9.1)
INSULIN ASPART	0	2 (9.5)	3 (13.6)	5 (11.6)	5 (7.6)
INSULIN DEGLUDEC	0	1 (4.8)	2 (9.1)	3 (7.0)	3 (4.5)
INSULIN LISPRO	2 (8.7)	0	0	0	2 (3.0)
PIOGLITAZONE	0	0	2 (9.1)	2 (4.7)	2 (3.0)
ALOGLIPTIN	1 (4.3)	0	0	0	1 (1.5)
EMPAGLIFLOZIN	0	0	1 (4.5)	1 (2.3)	1 (1.5)
EMPAGLIFLOZIN;LINAGLIPTIN;METFORMIN HYDROCHLORIDE	0	0	1 (4.5)	1 (2.3)	1 (1.5)
GLICLAZIDE	1 (4.3)	0	0	0	1 (1.5)
METFORMIN HYDROCHLORIDE;VILDAGLIPTIN	0	0	1 (4.5)	1 (2.3)	1 (1.5)
SITAGLIPTIN	1 (4.3)	0	0	0	1 (1.5)

Note 1: Background Medications were defined as any medications that patients were exposed to before first dose and continued after first dose of study drug.
Note 2: A patient was counted once for each medication category and preferred term even if multiple medications were reported by the patient.
Note 3: Percentages were based on the number of safety patients in each treatment group or overall.
Note 4: Background Medications were classified according to WHO-DDE version GLOBAL B3 MAR 2023.

Source Data: ADCM
Program name: t_adcm_background.sas Run date: 23JAN2024 02:21 Database last modified: 30AUG2023

- **Numbers analysed**

Primary analysis is based on the Full Analysis Set (n=66), which included all patients who were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. Per Protocol Set was a subset of the Full Analysis Set who received at least 5 monthly doses of olezarsen or placebo within the first 6 months (172 days) of the Treatment Period, and who had no significant protocol deviations that could compromise the interpretation of efficacy (n=59). The data cut-off was on 14 Jul 2023 (End of Treatment).

Table 17. Number of patients included in the analyses

	Placebo (N = 23) n (%)	Olezarsen 50 mg (N = 21) n (%)	Olezarsen 80 mg (N = 22) n (%)
Full Analysis Set [a]	23 (100)	21 (100)	22 (100)
Per Protocol Set [b]	22 (95.7)	18 (85.7)	19 (86.4)
Safety Set [c]	23 (100)	21 (100)	22 (100)
PK Set [d]	0	21 (100)	22 (100)

- **Outcomes and estimation**

The primary efficacy endpoint, percent change in fasting TG from Baseline at Month 6 (average of Weeks 23, 25, and 27) compared with placebo, was met in this study (Section 11.4.1.2). 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 (placebo-adjusted mean percent decrease from Baseline of 43.50% for olezarsen 80 mg; p = 0.0009). A placebo-adjusted mean percent decrease (22.37%) in fasting TG levels from Baseline at Month 6 (average of Weeks 23, 25, and 27) was observed for patients treated with olezarsen 50 mg once every 4 weeks; however, the difference in mean change from Baseline in fasting TG levels between the olezarsen 50 mg group and the placebo group did not reach statistical significance (p = 0.0775). Due to the hierarchical testing of endpoints described in the SAP, Version 4.0, 15 Aug 2023 (Appendix 16.1.9), subsequent endpoints were statistically considered exploratory.

Table 18. Mean Percent Change from Baseline in Fasting Triglycerides (mg/dL) at Month 6 (Full Analysis Set)

Analysis Endpoint	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Baseline: Mean (SD) [a]	2595.7 (1255.72)	2683.8 (1235.06)	2613.1 (1498.96)
Month 6: Mean (SD) [b]	2641.3 (1336.57)	2086.8 (807.48)	1731.9 (1204.26)
% Change from Baseline			
LSM (95% CI) [c]	11.52 (-5.321, 28.356)	-10.85 (-27.797, 6.095)	-31.99 (-49.031, -14.940)
---------- **Difference (Olezarsen - Placebo)** ----------			
LSM [c] (95% CI) [d]	--	-22.37 (-47.200, 2.463)	-43.50 (-69.085, -17.921)
p-value [d]	--	0.0775	0.0009

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

[a] Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification Period and Screening Period), prior to administration of the first dose of study drug.
[b] The primary analysis time point (Month 6) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[c] 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. The ANCOVA model included precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, treatment group, 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 TG as a covariate.
[d] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
Abbreviations: ANCOVA = analysis of covariates; CI = confidence interval; J2R = jump to reference;
LSM = least-squares mean; MAR = missing at random; MI = multiple imputation; SD = standard deviation; TG = triglycerides.

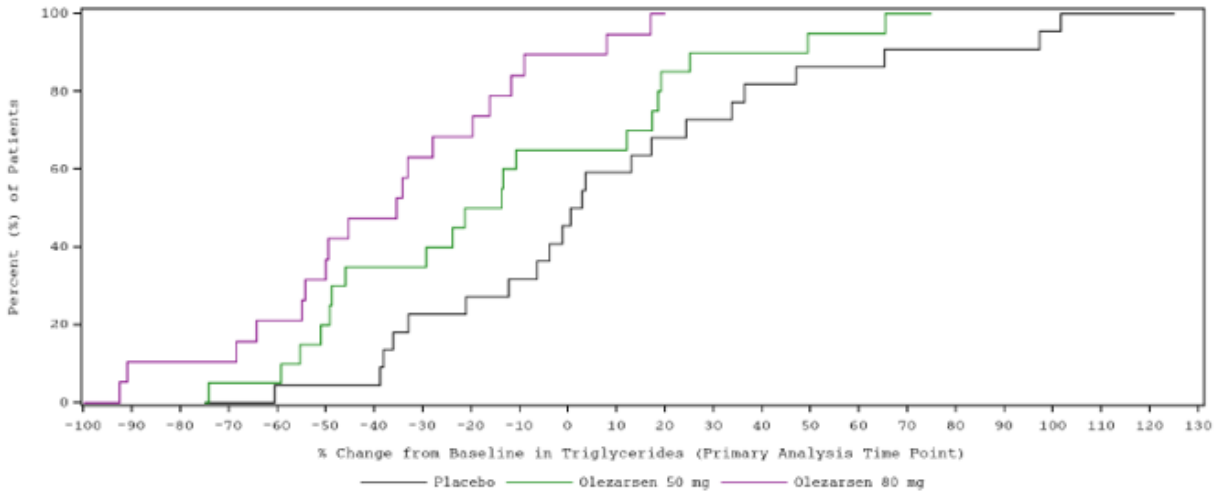


Figure 8. Cumulative Distribution Plot of Percent Change from Baseline in Fasting Triglycerides (mg/dL) at Month 6 (Full Analysis Set)

Primary efficacy endpoint results for the Full Analysis Set are summarized in Table 18 (mg/dL). Cumulative distribution for percent change from Baseline in fasting TG levels at Month 6 is presented in Figure 8. The waterfall plots of percent change from Baseline in fasting TG at Month 6 are presented in Figure 9.

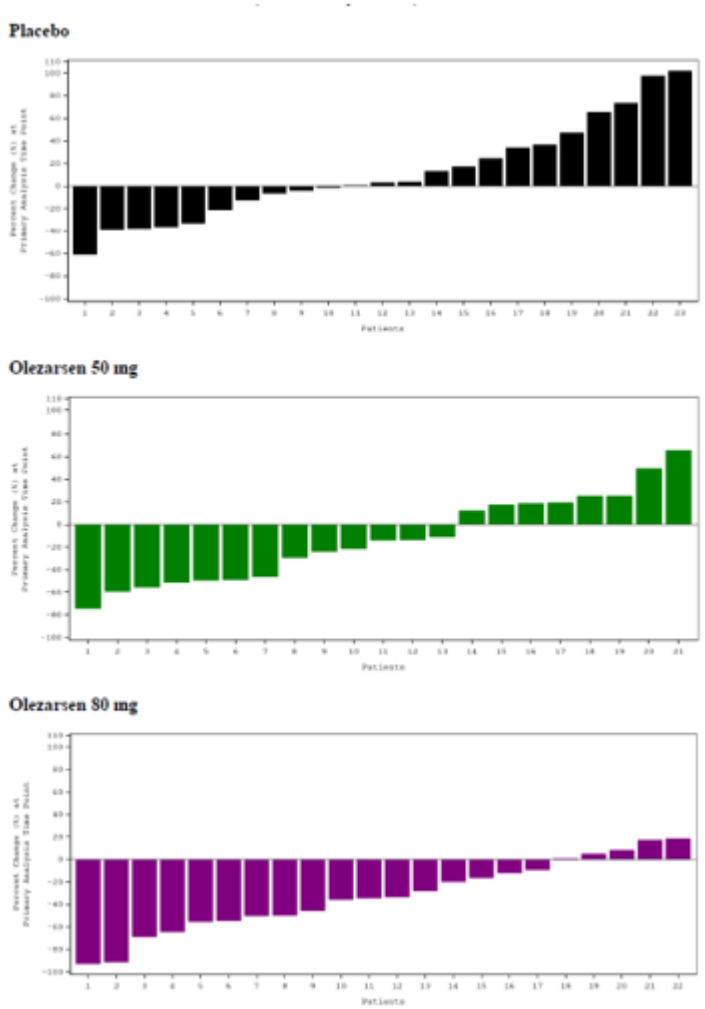


Figure 9. Waterfall Plot of Percent Change from Baseline in Fasting Triglycerides from Baseline at Month 6 (Full Analysis Set)

Secondary endpoints

Most subsequent endpoints (secondary efficacy endpoints) in the hierarchical testing sequence had nominally significant results.

For the olezarsen 80 mg group, the mean percent decrease in TG levels (placebo-adjusted) from Baseline at Month 12 was 59.39% (95% CI: -90.663, -28.119); the difference in mean percent decrease from Baseline in fasting TG levels at Month 12 for the olezarsen 80 mg group compared with placebo was nominally significant (nominal p-value = 0.0002). For the olezarsen 50 mg group, the mean percent decrease in TG levels (placebo-adjusted) from Baseline at Month 12 was 43.81% (95% CI: -73.928, -13.692); the difference in mean percent decrease from Baseline in TG levels for the olezarsen 50 mg group compared with placebo at Month 12 was nominally significant (p-value = 0.0044).

Table 19. Percent Change from Baseline in Fasting Triglycerides (mg/dL) at Month 12 (Full Analysis Set)

Analysis Endpoint	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Month 12 (Missing Data Imputed with Washout MI [c])			
Baseline: Mean (SD) [a]	2595.7 (1255.72)	2683.8 (1235.06)	2613.1 (1498.96)
Month 12: Mean (SD) [b]	2959.0 (1429.66)	2034.4 (961.19)	1589.9 (913.77)
% Change from Baseline at Month 12			
LSM (95% CI) [c]	20.89 (1.016, 40.764)	-22.92 (-42.505, -3.336)	-38.50 (-58.187, -18.815)
---------- **Difference (Olezarsen - Placebo)** ----------			
LSM [c] (95% CI) [d]	--	-43.81 (-73.928, -13.692)	-59.39 (-90.663, -28.119)
Nominal p-value [d]	--	0.0044	0.0002

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

[a] Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification Period and Screening Period), prior to administration of the first dose of study drug.

[b] Month 12 was defined as the average of Weeks 51 and 53. If 1 assessment was missing, then the other non-missing assessment was used.

[c] 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. The ANCOVA model included precent change from Baseline to Month 12 in fasting TG as dependent variable, treatment group, 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 TG as a covariate.

[d] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method. Abbreviations: ANCOVA = analysis of covariates; CI = confidence interval; J2R = jump to reference;

LSM = least-squares mean; MAR = missing at random; MI = multiple imputation; SD = standard deviation; TG = triglycerides.

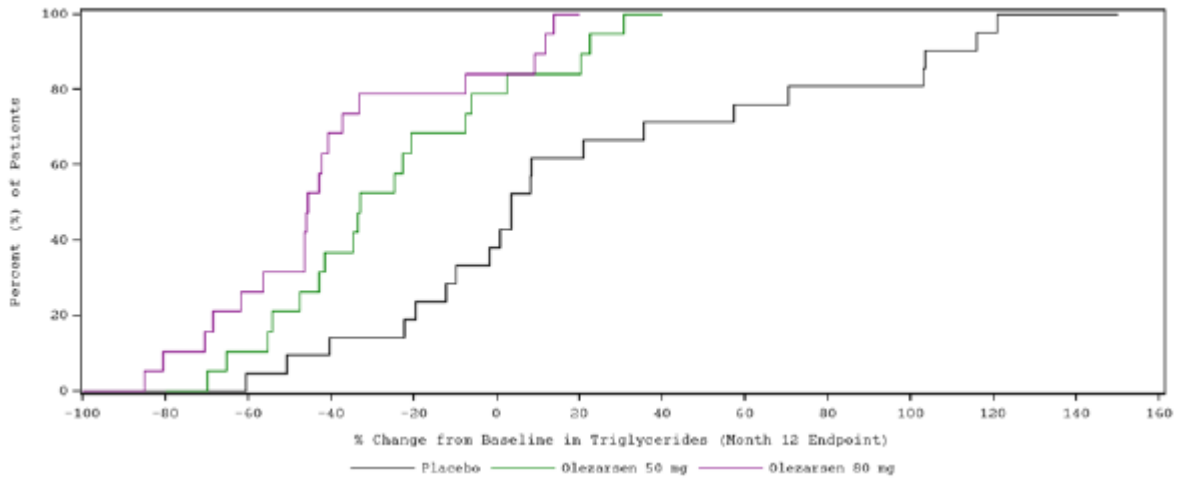


Figure 10. Cumulative Distribution of Percent Change from Baseline in Fasting Triglyceride Levels (mg/dL) at Month 12 (Full Analysis Set).

The summary of secondary endpoints results are provided in the Table 20.

Table 20. Secondary endpoints results

No.	Assessment	Placebo (n = 23)	Olezarsen 50 mg (n = 21)	Olezarsen 80 mg (n = 22)	Nominal p-value
1	**80 mg**: Percent Change in Fasting TG from Baseline to Month 12 (%)	20.89	--	-38.50	0.0002 [a]
2	**80 mg**: Percent Change in Fasting apoC-III from Baseline to Month 6 (%)	7.57	--	-66.13	< 0.0001 [a]
3	**80 mg**: Percent Change in Fasting apoC-III from Baseline to Month 12 (%)	17.08	--	-64.20	< 0.0001 [a]
4	**80 mg**: Proportion of Patients who Achieve ≥ 40% Decrease in Fasting TG from Baseline to Month 6 - n (%)	1 (4.3)	--	9 (40.9)	0.0183 [a]
5	**80 mg**: Percent Change in Fasting apoB-48 from Baseline to Month 6 (%)	24.50	--	-59.46	0.0019 [a]
6	**80 mg**: Percent Change in Fasting non-HDL-C from Baseline to Month 6 (%)	5.33	--	-18.86	0.0036 [a]
7	**50 mg**: Percent Change in Fasting TG from Baseline to Month 12 (%)	20.89	-22.92	--	0.0044 [a]
8	**50 mg**: Percent Change in Fasting apoC-III from Baseline to Month 6 (%)	7.57	-57.91	--	< 0.0001 [a]
9	**50 mg**: Percent Change in Fasting apoC-III from Baseline to Month 12 (%)	17.08	-59.98	--	< 0.0001 [a]
10	**50 mg**: Proportion of Patients who Achieve ≥ 40% Decrease in Fasting TG from Baseline to Month 6 - n (%)	1 (4.3)	7 (33.3)	--	0.0409 [a]
11	**50 mg**: Percent Change in Fasting apoB-48 from Baseline to Month 6 (%)	24.50	-8.78		0.1860
12	**50 mg**: Percent Change in Fasting non-HDL-C from Baseline to Month 6 (%)	5.33	-12.35	--	0.0401 [a]
13	**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	66.22	6.73		0.0052 [a]
14	**Total 80 mg and 50 mg**: Adjudicated Acute Pancreatitis Event Rate from Week 1 to Week 53 – LSM Event Rate	36.31	4.37		0.0144 [a]
15	**Total 80 mg and 50 mg (Prior History of Pancreatitis ≤ 10 Years Prior to Screening)**: Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 – LSM Event Rate	57.89	8.17		0.0174 [a]
16	**Total 80 mg and 50 mg**: Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 – LSM Event Rate	33.43	5.42		0.0314 [a]
17	**80 mg**: Proportion of Patients who Achieve ≥ 70% Decrease in Fasting TG from Baseline to Month 6 – n (%)	0	--	2 (9.1)	0.2802 [a]
18	**80 mg**: Percent Change in Fasting non-HDL-C from Baseline to Month 12 (%)	12.01	--	-27.69	0.0009 [a]
19	**80 mg**: Percent Change in Fasting apoB-48 from Baseline to Month 12 (%)	-3.52	--	-79.15	0.0560
20	**80 mg**: Proportion of Patients who Achieve Fasting TG ≤ 880 mg/dL at Month 6, n (%)	0	--	3 (14.3)	0.1885
21	**50 mg**: Proportion of Patients who Achieve ≥ 70% Decrease in Fasting TG from Baseline to Month 6 – n (%)	0	1 (4.8)	--	0.4494
22	**50 mg**: Percent Change in Fasting non-HDL-C from Baseline to Month 12 (%)	12.01	-17.84	--	0.0134 [a]
23	**50 mg**: Percent Change in Fasting apoB-48 from Baseline to Month 12 (%)	-3.52	-36.41	--	0.4219
24	**50 mg**: Proportion of Patients who Achieve Fasting TG ≤ 880 mg/dL at Month 6 – n (%)	0	2 (10.0)	--	0.2487
25	**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	118.59	16.59		0.0137 [a]
26	**Total 80 mg and 50 mg (≥ 2 Events in 5 Years Prior to Enrollment)**: Adjudicated Acute Pancreatitis Event Rate from Week 13 to Week 53 – LSM Event Rate	106.91	21.36		0.0480
27	**80 mg**: Proportion of Patients who Achieve fasting TG ≤ 500 mg/dL at Month 6 (%)	0	-	3 (13.6%)	0.2401
28	**50 mg**: Proportion of Patients who Achieve fasting TG ≤ 500 mg/dL at Month 6 (%)	0	0	-	0.9857

Note: Due to an error in the number of reported adjudicated pancreatitis events in the olezarsen 80 mg group as described in Section 9.8.2, a correction for this 1 event was made at the time of the final study database lock on 30 Nov 2023 (for patients who remained in Follow-up after the 30 Aug 2023 database lock). Therefore, data for the adjudicated pancreatitis events are from the 30 Nov 2023 database lock.
Note: Endpoints are in hierarchical sequence as described in the SAP, Version 4.0, 15 Aug 2023 (Appendix 16.1.9).
Note: All assessments are compared with the pooled placebo group.
Note: Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification Period and Screening Period), prior to administration of the first dose of study drug. Month 6 was the primary analysis time point and was defined as the average of Weeks 23, 25, and 27; if 1 or 2 of the 3 assessments were missing, then non-missing assessments were used. Month 12 was defined as the average of Weeks 51 and 53; if 1 assessment was missing, then the other non-missing assessment was used.
Note: Analyses for percent change are reported as least-squares mean percent changes.
[a] Nominal statistical significance ($p < 0.05$).
Abbreviations: apoB-48 = apolipoprotein B-48; apoC-III = apolipoprotein C-III; LSM = least-squares mean; non-HDL-C = non-high-density-lipoprotein cholesterol; TG = triglycerides.

Adjudicated acute pancreatitis

The adjudicated acute pancreatitis event rate from Week 1 to Week 53 in the subset of FAS with a prior history of pancreatitis within 10 years prior to Screening was compared between pooled treatment and placebo group using a Negative Binomial regression model. In this model the treatment group and previous treatment with volanesorsen (yes/no) were as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrolment and time, as a covariate. The logarithm of time in year that each patient was observed from Week 1 to Week 53 was used as an offset variable. From the models, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratio relative to the placebo group and corresponding 95% confidence intervals was estimated, the p-value of Wald-based chi-square test was also reported.

Adjudicated acute pancreatitis event rates are presented in Table 21 (Full Analysis Set), Table 22 (patients with a history of acute pancreatitis in 10 years prior to Screening), and Table 26 (patients with ≥ 2 adjudicated acute pancreatitis events in 5 years prior to enrolment).

Table 21. Adjudicated Acute Pancreatitis Event Rate (Full Analysis Set).

	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)	Total Olezarsen (N = 43)
Week 1 to 53 [a]				
Patients with Event from Week 1 to Week 53, n (%)	7 (30.4)	1 (4.8)	1 (4.5)	2 (4.7)
Number of Events	11	1	1	2
Total Patient Years	22.9	19.9	20.3	40.2
Mean event rate/100 patient years (95% CI)	36.31 (14.700, 89.685)	--	--	4.37 (0.942, 20.298)
---------- **Treatment Comparison: Olezarsen vs. Placebo** ----------				
Mean Rate Ratio - Olezarsen/Placebo (95% CI)	--	--	--	0.12 (0.022, 0.656)
Nominal p-value (negative binomial)	--	--	--	0.0144
Week 13 to Week 53 [b]				
Patients with Event from Week 13 to Week 53, n(%)	6 (26.1)	1 (4.8)	1 (4.5)	2 (4.7)
Number of Events	8	1	1	2
Total Patient Years	17.6	15.1	15.4	30.5
Mean event rate/100 patient years (95% CI)	33.43 (13.250, 84.321)	--	--	5.42 (1.229, 23.897)
---------- **Treatment Comparison: Olezarsen vs. Placebo** ----------				
Mean Rate Ratio - Olezarsen/Placebo (95% CI)	--	--	--	0.16 (0.031, 0.850)
Nominal p-value (negative binomial)	--	--	--	0.0314

Source: ISIS 678354-CS3 CSR, Table 14.2.2.5.2 and Table 14.2.2.6.2

Note: Due to an error in the number of reported adjudicated pancreatitis events in the olezarsen 80 mg group, a correction for this 1 event was made at the time of the final study database lock on 30 Nov 2023 (for patients who remained in Follow-up after the 30 Aug 2023 lock). Therefore, data for the adjudicated pancreatitis events are from the 30 Nov 2023 database lock.

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.

Table 22. Adjudicated Acute Pancreatitis Event Rate – Patients with History of Acute Pancreatitis in 10 Years Prior to Screening (Full Analysis Set).

	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)	Total Olezarsen (N = 43)
Patients with a prior history of pancreatitis within 10 years prior to screening	15	15	17	32
Week 1 to 53 [a]				
Patients with Event from Week 1 to Week 53, n(%)	7 (46.7)	1 (6.7)	1 (5.9)	2 (6.3)
Number of Events	11	1	1	2
Total Patient Years	14.8	13.7	16.2	29.9
Mean event rate/100 patient years (95% CI)	66.22 (30.490, 143.817)	--	--	6.73 (1.612, 28.087)
---------- Treatment Comparison: Olezarsen vs. Placebo ----------				
Mean Rate Ratio - Olezarsen/Placebo (95% CI)	--	--	--	0.10 (0.020, 0.506)
Nominal p-value (negative binomial)	--	--	--	0.0052
Week 13 to Week 53 [b]				
Patients with Event from Week 13 to Week 53, n(%)	6 (40.0)	1 (6.7)	1 (5.9)	2 (6.3)
Number of Events	8	1	1	2
Total Patient Years	11.3	10.4	12.2	22.6
Mean event rate/100 patient years (95% CI)	57.89 (24.469, 136.972)			8.17 (1.952, 34.177)
---------- Treatment Comparison: Olezarsen vs. Placebo ----------				
Mean Rate Ratio - Olezarsen/Placebo (95% CI)	--	--	--	0.14 (0.028, 0.709)
Nominal p-value (negative binomial)	--	--	--	0.0174

Source: Table 14.2.2.5.1 and Table 14.2.2.6.1

Note: Due to an error in the number of reported adjudicated pancreatitis events in the olezarsen 80 mg group as described in Section 9.8.2, a correction for this 1 event was made at the time of the final study database lock on 30 Nov 2023 (for patients who remained in Follow-up after the 30 Aug 2023 lock). Therefore, data for the adjudicated pancreatitis events are from the 30 Nov 2023 database lock.

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.

[a] The logarithm of time in year that each patient was observed from Week 1 to Week 53 or early termination was used as an offset variable. If the Negative Binomial regression model didn't converge, a Poisson regression model with Pearson chi-square scaling of standard errors to account for potential overdispersion was used instead of the Negative Binomial regression model. The model included the same factors and covariate as the Negative Binomial regression model.

[b] The logarithm of time in year that each patient was observed from Week 13 to Week 53 or early termination was used as an offset variable. Event rates of patients who discontinued before Week 13 were prorated based on the adjudicated acute pancreatitis events in 5 years prior to the enrollment over 294 days (Week 53 Day 379 – Week 13 Day 85). If the Negative Binomial regression model didn't converge, a Poisson regression model with Pearson chi-square scaling of standard errors to account for potential overdispersion was used instead of the Negative

Table 23. *Adjudicated Acute Pancreatitis Event Rate – Patients with ≥ 2 Adjudicated Acute Pancreatitis Events in 5 Years Prior to Enrolment (Full Analysis Set).*

	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)	Total Olezarsen (N = 43)
Patients with ≥ 2 adjudicated acute pancreatitis events in 5 years prior to enrollment	9	6	6	12
Week 1 to 53 [a]				
Patients with Event from Week 1 to Week 53, n (%)	6 (66.7)	1 (16.7)	1 (16.7)	2 (16.7)
Number of Events	10	1	1	2
Total Patient Years	8.7	5.5	6.1	11.7
Mean event rate/100 patient years (95% CI)	118.59 (61.226, 229.698)	--	--	16.59 (4.051, 67.948)
---------- Treatment Comparison: Olezarsen vs. Placebo ----------				
Mean Rate Ratio - Olezarsen/Placebo (95% CI)	--	--	--	0.14 (0.029, 0.669)
Nominal p-value (negative binomial)	--	--	--	0.0137
Week 13 to Week 53 [b]				
Patients with Event from Week 13to Week 53, n (%)	5 (55.6)	1 (16.7)	1 (16.7)	2 (16.7)
Number of Events	7	1	1	2
Total Patient Years	6.6	4.1	4.8	8.9
Mean event rate/100 patient years (95% CI)	106.91 (50.204, 227.682)			21.36 (5.233, 87.219)
---------- Treatment Comparison: Olezarsen vs. Placebo ----------				
Mean Rate Ratio - Olezarsen/Placebo (95% CI)	--	--	--	0.20 (0.040, 0.986)
Nominal p-value (Poisson regression)	--	--	--	0.0480

Source: Table 14.2.2.7.1 and Table 14.2.2.7.2
Note: Due to an error in the number of reported adjudicated pancreatitis events in the olezarsen 80 mg group as described in Section 9.8.2, a correction for this 1 event was made at the time of the final study database lock on 30 Nov 2023 (for patients who remained in Follow-up after the 30 Aug 2023 lock). Therefore, data for the adjudicated pancreatitis events are from the 30 Nov 2023 database lock.
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.
[a] The logarithm of time in year that each patient was observed from Week 1 to Week 53 or early termination was used as an offset variable. If the Negative Binomial regression model didn't converge, a Poisson regression model with Pearson chi-square scaling of standard errors to account for potential overdispersion was used instead of the Negative Binomial regression model. The model included the same factors and covariate as the Negative Binomial regression model.
[b] The logarithm of time in year that each patient was observed from Week 13 to Week 53 or early termination was used as an offset variable. Event rates of patients who discontinued before Week 13 were prorated based on the

- **Ancillary analyses**

Sensitivity analyses

Six sensitivity analyses were conducted on the primary efficacy endpoint (mean percent change in fasting TG from Baseline at Month 6), including analysis of the Per Protocol Set, analysis of a subgroup of the Full Analysis Set that had no missing TG values at Month 6, assessment of the robustness of the primary analysis for the Full Analysis Set, non-parametric analysis with Wilcoxon rank-sum test for the Full Analysis Set, tipping point for the Full Analysis Set, and an ANCOVA model using log-transformed data for the Full Analysis Set.

The primary efficacy endpoints were assessed on with sensitivity analysis on the Per Protocol Set, its results are presented below.

Table 24. Sensitivity analysis of percent change from baseline in fasting TG (mmol/L) at primary analysis time point (Per Protocol Set).

Analysis Endpoint	Statistic	Placebo (N=22)	Olezarsen 50 mg (N=18)	Olezarsen 80 mg (N=19)
Primary Analysis Time Point [3]				
	N	22	18	19
Baseline [1]	Mean (SD)	29.650 (14.4396)	32.115 (14.2617)	30.281 (17.9967)
Primary Analysis Time Point [2]	Mean (SD)	29.443 (15.3311)	23.515 (9.7830)	18.464 (14.1471)
% Change from Baseline				
	LSM [3]	8.21	-16.05	-37.83
	(95% CI) [3]	(-7.111, 23.529)	(-33.293, 1.184)	(-55.366, -20.303)

SD = standard deviation; LSM = least squares mean; CI = confidence intervals
[1] Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug.
[2] The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[3] The ANCOVA model included precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, treatment group, 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 TG as a covariate.
[4] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
[5] Normality was tested based on observed data.

Analysis Endpoint	Statistic	Placebo (N=22)	Olezarsen 50 mg (N=18)	Olezarsen 80 mg (N=19)
---------- Difference (Active -Placebo) ----------				
	LSM [3]		-24.26	-46.04
	(95% CI) [4]		(-47.400, -1.126)	(-69.232, -22.854)
	p-value [4]		0.0404	0.0003
---------- Shapiro-Wilk Normality Test [5] ----------				
	p-value		0.1155	

SD = standard deviation; LSM = least squares mean; CI = confidence intervals
[1] Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug.
[2] The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[3] The ANCOVA model included precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, treatment group, 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 TG as a covariate.
[4] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
[5] Normality was tested based on observed data.

Source Data: ADEFF
Program name: t_adeff_pchg.sas Run date: 23JAN2024 02:21 Database last modified: 30AUG2023

Table 25. Sensitivity analysis of percent change from baseline in fasting TG (mmol/L) at primary analysis time point (subset patients with non-missing endpoints).

Table 14.2.1.1.13
Sensitivity Analysis of Percent Change from Baseline in Fasting Triglycerides (mmol/L) at Primary Analysis Time Point - Subset of Patients with Non-missing Endpoints - SI Unit
Full Analysis Set (N=66)

Analysis Endpoint	Statistic	Placebo (N=23)	Olezarsen 50 mg (N=21)	Olezarsen 80 mg (N=22)
Primary Analysis Time Point [3]				
	N	22	20	19
Baseline [1]	Mean (SD)	29.650 (14.4396)	31.042 (13.9166)	30.281 (17.9967)
Primary Analysis Time Point [2]	Mean (SD)	29.443 (15.3311)	23.759 (9.3231)	18.464 (14.1471)
% Change from Baseline				
	LSM [3]	8.11	-12.41	-38.04
	(95% CI) [3]	(-7.157, 23.383)	(-28.848, 4.036)	(-55.501, -20.576)

SD = standard deviation; LSM = least squares mean; CI = confidence intervals
[1] Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug.
[2] The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[3] Subset of the patients in the FAS with no missing TG values at primary analysis time point. The ANCOVA model included precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, treatment group, 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 TG as a covariate.
[4] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
[5] Normality was tested based on observed data.

Sensitivity Analysis of Percent Change from Baseline in Fasting Triglycerides (mmol/L) at Primary Analysis Time Point - Subset of Patients with Non-missing Endpoints - SI Unit
Full Analysis Set (N=66)

Analysis Endpoint	Statistic	Placebo (N=23)	Olezarsen 50 mg (N=21)	Olezarsen 80 mg (N=22)
---------- Difference (Active -Placebo) ----------				
	LSM [3]		-20.52	-46.15
	(95% CI) [4]		(-43.031, 1.992)	(-69.278, -23.026)
	p-value [4]		0.0728	0.0003
---------- Shapiro-Wilk Normality Test [5] ----------				
	p-value		0.1109	

SD = standard deviation; LSM = least squares mean; CI = confidence intervals
[1] Baseline was defined as the average of the pre-dose measurement on Day 1 and the last non-missing measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug.
[2] The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[3] Subset of the patients in the FAS with no missing TG values at primary analysis time point. The ANCOVA model included precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, treatment group, 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 TG as a covariate.
[4] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
[5] Normality was tested based on observed data.

Table 26. Sensitivity analysis of percent change from baseline in fasting TG (mmol/L) at primary analysis time point (pattern mixture models with ANCOVA, FAS)).

Analysis Endpoint [1] Approach	Statistic [2]	Placebo (N=23)	Olezarsen 50 mg (N=21)	Olezarsen 80 mg (N=22)
Primary Analysis Time Point Analysis to Compare Olezarsen vs. Placebo Approach 1: Informative missing patients treated with olezarsen have missing post-treatment discontinuation values imputed using the copy increment from reference (CIR) approach. Otherwise, non-informative missing data are imputed under the MAR assumption.				
	LSM	11.64	-11.92	-34.37
	(95% CI)	(-7.451, 30.737)	(-31.709, 7.874)	(-63.460, -5.277)
	Difference in LSM (Active - Placebo)		-23.56	-46.01
	(95% CI) [3]		(-48.528, 1.407)	(-83.041, -8.982)
	p-value [3]		0.0644	0.0149

LSM = least squares mean; CI = confidence intervals
[1] Baseline was defined as the average of the pre-dose measurement on Day 1 and the non-missing last measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug. The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[2] For each imputed data set, an ANCOVA model with percent change from baseline as the dependent variable, treatment group, two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with Volanesorsen (yes vs. no) and treatment group (olezarsen 80 mg, olezarsen 50 mg, placebo) as factors, and log-transformed baseline as a covariate was fitted. The LS means, confidence intervals, and p-values presented in the table were the overall estimates combined from the imputed data.
[3] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Analysis Endpoint [1] Approach	Statistic [2]	Placebo (N=23)	Olezarsen 50 mg (N=21)	Olezarsen 80 mg (N=22)
Approach 2: All patients treated with olezarsen who discontinue the study have missing post-treatment discontinuation values imputed using the CIR approach.				
	LSM	11.55	-12.05	-35.14
	(95% CI)	(-4.880, 27.978)	(-28.546, 4.449)	(-51.753, -18.534)
	Difference in LSM (Active - Placebo)		-23.60	-46.69
	(95% CI) [3]		(-48.257, 1.062)	(-71.675, -21.710)
	p-value [3]		0.0607	0.0002

LSM = least squares mean; CI = confidence intervals
[1] Baseline was defined as the average of the pre-dose measurement on Day 1 and the non-missing last measurement closest to Day 1 (last measurements from Qualification period and Screening period), prior to administration of the first dose of Study Drug. The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used.
[2] For each imputed data set, an ANCOVA model with percent change from baseline as the dependent variable, treatment group, two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with Volanesorsen (yes vs. no) and treatment group (olezarsen 80 mg, olezarsen 50 mg, placebo) as factors, and log-transformed baseline as a covariate was fitted. The LS means, confidence intervals, and p-values presented in the table were the overall estimates combined from the imputed data.
[3] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.

Ad hoc analyses

Ad hoc analyses of the average percent change from Baseline in fasting TG levels for Week 1 through Week 53 and Week 13 through Week 53 were conducted by calculating the area under the curve (AUC) in the percent change from Baseline after the first dose of study drug (or Week 13) to the

earlier of Week 53 or last available visit and then divided by the number of days used for the AUC calculation for each patient, resulting in the percent change per day values. The ad hoc analyses of the average percent change from Baseline in fasting TG levels for all measurements from Week 1 through Week 53 and Week 13 through Week 53 are summarized in Table 27 below.

Table 27: Ad Hoc Analysis of Average Percent Change from Baseline in Fasting Triglyceride Levels at Month 12

Analysis	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Average % Change from Baseline in TG Levels from Week 1 Through Week 53 [a,b]			
n	23	21	21
Mean (SD)	17.0 (40.42)	-22.1 (31.06)	-38.2 (24.85)
LSM (95% CI) [c]	14.5 (1.54, 27.46)	-23.3 (-37.13, -9.45)	-41.2 (-55.55, -26.83)
---------- **Difference (Olezarsen - Placebo)** ----------			
LSM[c] (95% CI) [d]	--	-37.8 (-56.15, -19.43)	-55.7 (-74.19, -37.20)
Nominal p-value [d]	--	0.0001	< 0.0001
Average % Change from Baseline in TG Levels from Week 13 Through Week 53 [a,b]			
n	23	20	21
Mean (SD)	19.6 (45.13)	-22.9 (29.49)	-38.6 (27.60)
LSM (95% CI) [c]	16.3 (2.46, 30.23)	-23.7 (-38.91, -8.56)	-42.6 (-58.01, -27.23)
---------- **Difference (Olezarsen - Placebo)** ----------			
LSM[c] (95% CI) [d]	--	-40.1 (-60.04, -20.11)	-59.0 (-78.76, -39.16)
Nominal p-value [d]	--	0.0002	< 0.0001

a-Patients with no post Baseline data (or after Week 13) were excluded from the analysis.

b-Average percent change from Baseline in fasting TG levels equals the area under the concentration time curve of TG percent change divided by days of the corresponding Treatment Period.

c- The LSMs and their 95% CI were estimated from an ANCOVA model with treatment group and 2 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 TG as a covariate.

d -The 95% CIs of treatment difference and p values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
Abbreviations: ANCOVA = analysis of covariates; CI = confidence interval; CSR = clinical study report; LSM = least squares mean; SD = standard deviation; TG = triglyceride.

Ad hoc analyses of average percent change from Baseline in apoC-III levels for all measurements from Week 1 Through Week 53 and Week 13 to Week 53 are presented below (Table 28).

Table 28: Ad Hoc Analysis of Average Percent Change from Baseline in Fasting Apolipoprotein C-III levels from Week 1 Through Week 53 and Week 13 to Week 53 (Full Analysis Set).

Analysis	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)
Average % Change from Baseline in apoC-III Levels from Week 1 Through Week 53 [a]			
n	23	21	21
Mean (SD)	6.5 (16.74)	-55.7 (16.66)	-67.6 (17.39)
LSM (95% CI) [b]	6.5 (0.07, 12.89)	-55.4 (-62.28, -48.53)	-68.2 (-75.32, -61.10)
---------- **Difference (Olezarsen - Placebo)** ----------			
LSM [b] (95% CI) [c]	--	-61.9 (-70.97, -52.79)	-74.7 (-83.85, -65.52)
Nominal p-value [c]	--	< 0.0001	< 0.0001
Average % Change from Baseline in apoC-III Levels from Week 13 Through Week 53 [a]			
n	23	20	21
Mean (SD)	8.0 (19.64)	-61.5 (16.70)	-72.1 (17.94)
LSM (95% CI) [b]	8.0 (0.66, 15.28)	-61.2 (-69.24, -53.18)	-72.7 (-80.80, -64.58)
---------- **Difference (Olezarsen - Placebo)** ----------			
LSM [c] (95% CI) [d]	--	-69.2 (-79.69, -58.68)	-80.7 (-91.11, -70.22)
Nominal p-value [d]	--	< 0.0001	< 0.0001

[a] Patients with no post-Baseline data (or after Week 13) excluded from the analysis.
[b] Average percent change from Baseline in fasting apoC-III levels equals the area under the concentration-time curve (AUC) of apoC-III percent change divided by days of the corresponding treatment period.
[c] The LSMs and their 95% CI were estimated from an ANCOVA model with treatment group and 2 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 apoC-III as a covariate.
[d] The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
Abbreviations: ANCOVA = analysis of covariates; apoC-III = apolipoprotein C-III; CI = confidence interval; LSM = least-squares mean.

An ad hoc analysis of the proportion of patients who had an event of adjudicated acute pancreatitis from Week 1 to Week 53 was conducted in the Full Analysis Set, in the subset of patients with a prior history of pancreatitis within 10 years prior to Screening, and in the subset of patients with ≥ 2 events of adjudicated pancreatitis in 5 years prior to enrollment. The same analysis was repeated for patients who had an event of adjudicated acute pancreatitis from Week 13 to Week 53. Kaplan-Meier curves of time to first adjudicated acute pancreatitis event is provided for the FAS in ad hoc is presented below (Figure 11).

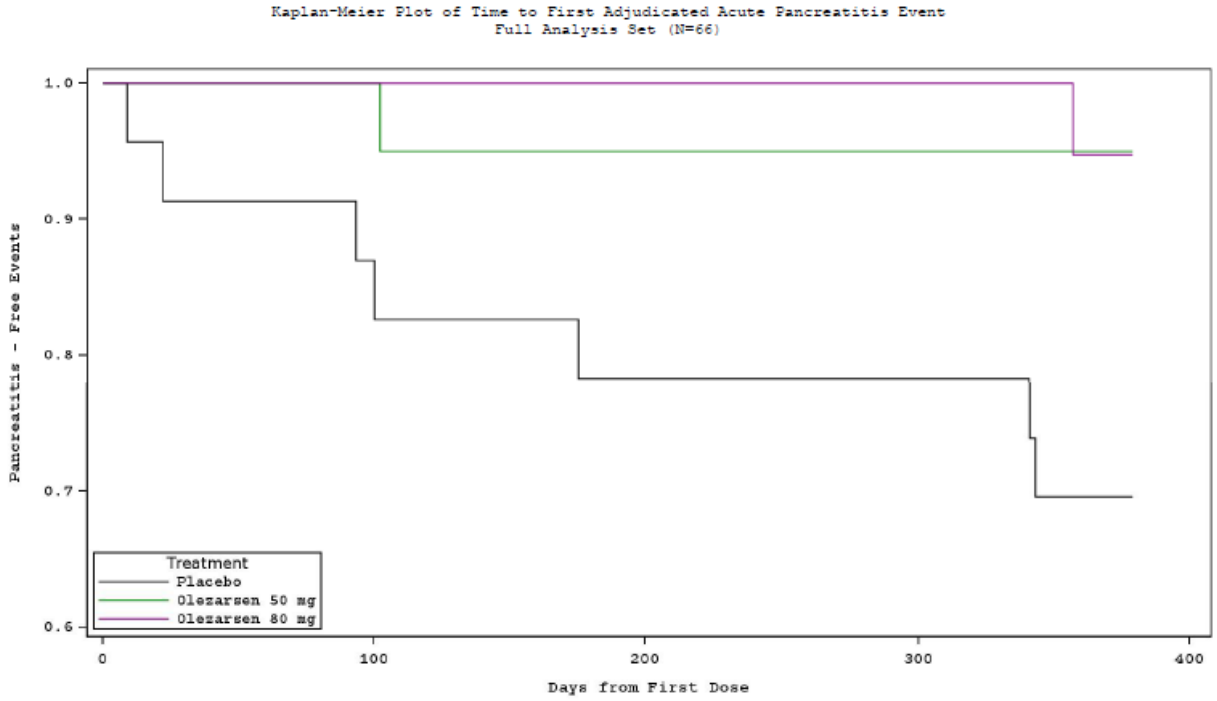


Figure 11. Kaplan-Meier curves of time to first adjudicated acute pancreatitis event in ad hoc (FAS)

An ad hoc analysis of the proportion of patients who had an event of adjudicated acute pancreatitis from Week 1 to Week 53 was conducted in the Full Analysis Set, in the subset of patients with a prior history of pancreatitis within 10 years prior to Screening, and in the subset of patients with ≥ 2 events of adjudicated pancreatitis in 5 years prior to enrolment. The same analysis was repeated for patients who had an event of adjudicated acute pancreatitis from Week 13 to Week 53. Overall, the discordance of classification of acute pancreatitis events was low. Of 31 adjudicated prospective events (during the study), one event in a patient in the placebo group was discordant in classification between adjudicator 1, who classified the event as pancreatitis, and adjudicator 2, who classified the event as not pancreatitis. The event was resolved in a meeting following the adjudication process/workflow described in the Pancreatitis Adjudication Charter, classifying the event as pancreatitis.

Table 29. Ad Hoc Analysis of Proportion of Patients with Pancreatitis Events (Full Analysis Set)

Analysis to Compare Treatment Group vs. Placebo in Incidence Rate [a]	Olezarsen 50 mg (N = 21) Nominal P-value	Olezarsen 80 mg (N = 22) Nominal P-value	Total Olezarsen (N = 43) Nominal P-value
All Patients			
Proportion of Patients with Acute Pancreatitis Event from Week 1 to Week 53	0.0481[c]	0.0470[c]	0.0066[c]
Proportion of Patients with Acute Pancreatitis Event from Week 13 to Week 53 [b]	0.1003	0.0973	0.0211[c]
Patients with A Prior History of Pancreatitis within 10 Years Prior to Screening			
Proportion of Patients with Acute Pancreatitis Event from Week 1 to Week 53	0.0352[c]	0.0133[c]	0.0025[c]
Proportion of Patients with Acute Pancreatitis Event from Week 13 to Week 53 [b]	0.0801	0.0330[c]	0.0097[c]
Patients with ≥ 2 Events of Adjudicated Acute Pancreatitis in 5 Years Prior to Enrollment			
Proportion of Patients with Acute Pancreatitis Event from Week 1 to Week 53	0.1189	0.1189	0.0318[c]
Proportion of Patients with Acute Pancreatitis Event from Week 13 to Week 53 [b]	0.2867	0.2867	0.1588

Source: Ad hoc Table 14.2.2.8.1

[a] The proportion of patients with an adjudicated pancreatitis event from Week 1 and Week 13 to Week 53 was compared between each olezarsen treatment group (olezarsen 80 mg, olezarsen 50 mg) and pooled olezarsen treatment group vs. pooled placebo group using a Fisher's exact test.

[b] Patients terminated before Week 13 were excluded from the analysis.

[c] Reached nominal statistical significance (p-value < 0.05).

Retrospective review of the acute pancreatitis events that in the placebo group there was the higher share of documented event of pancreatitis (52.2%) compared to the total olezarsen (39.6%) and specifically the 80 mg olezarsen group (36.4%).

*Table 30. A*cute pancreatitis *event reported as part of medical history.*

Table 14.2.2.9.1
Classification of Acute Pancreatitis Event by Different Adjudicators
Full Analysis Set (N=66)

Retrospective events

	Placebo (N=23) n (%) Events	Olezarsen 50 mg (N=21) n (%) Events	Olezarsen 80 mg (N=22) n (%) Events	Total Olezarsen (N=43) n (%) Events
Final Adjudication Committee				
Documented Pancreatitis	12 (52.2) 35	9 (42.9) 17	8 (36.4) 13	17 (39.5) 30
Probable Pancreatitis	1 (4.3) 1	3 (14.3) 3	2 (9.1) 2	5 (11.6) 5
Possible Pancreatitis	4 (17.4) 9	7 (33.3) 15	3 (13.6) 3	10 (23.3) 18
Insufficient (Unable to Adjudicate)	4 (17.4) 40	3 (14.3) 5	8 (36.4) 20	11 (25.6) 25
Not Documented (No Diagnosis of Acute Pancreatitis)	1 (4.3) 1	0	1 (4.5) 1	1 (2.3) 1

Note 1: Percentages were based on the number of patients in each treatment group. Note 2: Documented Pancreatitis: Pancreatitis that conforms to the revised Atlanta diagnostic criteria for acute pancreatitis. Probable Pancreatitis: Pancreatitis according to documentation of typical clinical features plus abnormal amylase/lipase (<3XULN). Possible Pancreatitis: Pancreatitis according to documentation of typical clinical features in subject with known history of pancreatitis. Insufficient (Unable to adjudicate): Insufficient source documentation provided (events that could not be placed in any of the preceding categories based on the available information) or not possible to adjudicate. Not Documented (No diagnosis of acute pancreatitis): Sufficient evidence provided to conclude that there was no diagnosis of acute pancreatitis during this hospitalization. Note 3: Retrospective events encompassed events reported as part of medical history. Prospective events included those that occurred during the study.

Pre-specified subgroup analysis

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

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

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial 678354-CS3 (Balance study)

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31. Summary of efficacy for trial 678354-CS3

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)		
Study identifier	Protocol number: ISIS 678354-CS3 EudraCT number: 2020-002536-67	
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled, 53-week study of olezarsen 50 mg or 80 mg or matching placebo administered once every 4 weeks in patients with familial chylomicronemia syndrome (FCS)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment period: 53 weeks Screening period: 4 to 8 weeks Diet stabilization/Run-in period: 2 weeks Post-treatment evaluation: 13 weeks (for patients that did not participate in the open-label extension study)
Hypothesis	Superiority	
Treatments groups	Olezarsen 80 mg	Patients randomly assigned to receive olezarsen 80 mg every 4 weeks.

	Olezarsen 50 mg		Patients randomly assigned to receive olezarsen 50 mg every 4 weeks.
	Placebo		Patients randomly assigned to receive placebo every 4 weeks; placebo results were pooled across both study groups for analysis.
Endpoints and definitions	Primary endpoint	TG Month 6 – 80 mg	Comparison of percent change in fasting triglycerides (TG) from Baseline to Month 6 between olezarsen 80 mg group and pooled placebo in the Full Analysis Set
	Primary endpoint	TG Month 6 –50 mg	Comparison of percent change in fasting TG from Baseline to Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 1	TG Month 12 – 80 mg	Comparison of percent change in fasting TG from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 2	apoC-III Month 6 – 80 mg	Comparison of percent change in fasting apolipoprotein C-III (apoC-III) from Baseline to Month 6 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 3	apoC-III Month 12 – 80 mg	Comparison of percent change in fasting apoC-III from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 4	≥ 40% reduction TG Month 6 – 80 mg	Comparison of proportion of patients who achieve ≥40% reduction in fasting TG from Baseline to Month 6 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 5	apoB 48 Month 6 – 80 mg	Comparison of percent change in fasting apolipoprotein B 48 (apoB-48) from Baseline to Month 6 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 6	Non-HDL-C Month 6 – 80 mg	Comparison of percent change in fasting non-high density lipoprotein cholesterol (non-HDL-C) from Baseline to Month 6 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 7	TG Month 12 – 50 mg	Comparison of percent change in fasting TG from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 8	apoC-III Month 6 – 50 mg	Comparison of percent change in fasting apoC-III from Baseline to Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 9	apoC-III Month 12 – 50 mg	Comparison of percent change in fasting apoC-III from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 10	≥ 40% reduction TG Month 6 – 50 mg	Comparison of proportion of patients who achieve ≥ 40% reduction in fasting TG from Baseline to Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set

	Secondary Endpoint 11	apoB-48 Month 6 – 50 mg	Comparison of percent change in fasting apoB-48 from Baseline to Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 12	Non-HDL-C Month 6 – 50 mg	Comparison of percent change in fasting non-HDL-C from Baseline to Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 13	Adjudicated pancreatitis to Week 1 to 53 – pooled olezarsen with a prior history of pancreatitis within 10 years	Comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with a prior history of pancreatitis within 10 years prior to Screening
	Secondary Endpoint 14	Adjudicated pancreatitis Week 1 to 53 – pooled olezarsen	Comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between pooled olezarsen treatment group and pooled placebo in Full Analysis Set
	Secondary Endpoint 15	Adjudicated pancreatitis to Week 13 to 53 – pooled olezarsen with a prior history of pancreatitis within 10 years	Comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with a prior history of pancreatitis within 10 years prior to Screening
	Secondary Endpoint 16	Adjudicated pancreatitis Week 13 to 53 – pooled olezarsen	Comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the Full Analysis Set
	Secondary Endpoint 17	≥70% reduction in TG from Baseline to Month 6 – 80 mg	Comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to Month 6 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 18	Non-HDL-C Month 12 – 80 mg	Comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 19	apoB-48 Month 12 – 80 mg	Comparison of percent change in fasting apoB-48 from Baseline to Month 12 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 20	TG ≤ 880 mg/dL at Month 6 – 80 mg	Comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at Month 6 between olezarsen 80 mg group and pooled placebo in the Full Analysis Set
	Secondary Endpoint 21	≥ 70% reduction in TG from Baseline to Month 6 – 50 mg	Comparison of proportion of patients who achieve ≥ 70% reduction in fasting TG from Baseline to Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 22	Non-HDL-C Month 12 – 50 mg	Comparison of percent change in fasting non-HDL-C from Baseline to Month 12 between olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 23	apoB-48 Month 12 – 50 mg	Comparison of percent change in fasting apoB-48 from Baseline to Month 12 between

			olezarsen 50 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 24	TG ≤ 880 mg/dL at Month 6 – 50 mg	Comparison of proportion of patients who achieve fasting TG ≤ 880 mg/dL at Month 6 between olezarsen 50 mg group and pooled placebo in the Full Analysis Set
	Secondary Endpoint 25	Adjudicated pancreatitis Week 1 to 53 – pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment	Comparison of adjudicated acute pancreatitis event rate from Week 1 to Week 53 between the pooled olezarsen treatment group and the pooled placebo in the subset of Full Analysis Set with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrolment
	Secondary Endpoint 26	Adjudicated pancreatitis Week 13 to 53 – pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment	Comparison of adjudicated acute pancreatitis event rate from Week 13 to Week 53 between pooled olezarsen treatment group and pooled placebo in the subset of Full Analysis Set with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrolment
	Secondary Endpoint 27	TG ≤ 500 mg/dL at Month 6 – 80 mg	Comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at the Month 6 between olezarsen 80 mg group and pooled placebo in Full Analysis Set
	Secondary Endpoint 28	TG ≤ 500 mg/dL at Month 6 – 50 mg	Comparison of proportion of patients who achieve fasting TG ≤ 500 mg/dL at Month 6 between olezarsen 50 mg group and pooled placebo in Full Analysis Set

Database lock	Database lock was on 30 Aug 2023
Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	Full Analysis Set: All patients who were randomly assigned to treatment and received any amount of olezarsen or placebo.

Descriptive statistics and estimate variability	Treatment group	Olezarsen 80 mg	Olezarsen 50 mg	Placebo
	Number of subjects	22	21	23
Primary Endpoints	TG Month 6 – 80 mg % Change from Baseline Least Square Mean (LSM)	**-31.99**	--	11.52
	95% CI	-49.031, -14.940	--	5.321, 28.356
	TG Month 6 – 50 mg % Change from Baseline, LSM	--	**-10.85**	11.52
	95% CI		-27.797, 6.095	-5.321, 28.356 --

Effect estimate per comparison	Primary endpoints	Test statistic	Treatment Group
	TG Month 6 – 80 mg	Difference	Olezarsen 80 mg

		(olezarsen-placebo)	
		Placebo-adjusted % Change from Baseline LSM	**-43.50**
		95% CI	-69.085, -17.921
		P-value (analysis of covariance [ANCOVA])	0.0009
	TG Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-22.37
		95% CI	-47.200, 2.463
		P-value (ANCOVA)	0.0775

Notes	The primary efficacy endpoint, percent change in fasting TG levels from Baseline at Month 6 (average of Weeks 23, 25, and 27) compared with placebo, was for the olezarsen 80 mg group, a placebo-adjusted mean percent decrease in fasting TG levels from Baseline at Month 6 of 43.50% (95% CI: -69.085, -17.921) was observed following treatment at Month 6. Compared with the placebo group, the mean percent decrease in TG levels in the olezarsen 80 mg group was statistically significant (**p = 0.0009**). A placebo-adjusted mean percent decrease in fasting TG levels from Baseline at Month 6 was observed for patients in the olezarsen 50 mg group (22.37% decrease [95% CI: -47.200, -2.463]); however, the difference in fasting TG levels between the olezarsen 50 mg group and the placebo group did not reach statistical significance (**p = 0.0775**). Review of TG levels over time for the olezarsen 50 mg group showed substantial decreases at all time points except at Week 27 (1 of the 3 time points averaged for the 6 month level), where mean values sharply deviated from the overall pattern observed over the course of the 12-month treatment period. At Month 12 (secondary endpoint 7 defined below), a placebo-adjusted mean percent decrease from Baseline of 43.81% (95% CI: -73.928, -13.692) was observed; the difference in mean percent change from Baseline compared with placebo at Month 12 was nominally significant (nominal p value = 0.0044). To control the overall Type I error rate at 0.05 across the primary endpoints and secondary endpoints for the final analysis, the gatekeeping testing strategy was applied to the primary and secondary endpoint families. The hierarchical testing procedure was utilized within the primary endpoint family and secondary endpoint family. **Due to this predefined hierarchical testing of endpoints, subsequent secondary endpoints were statistically considered exploratory.**
Analysis description	**Secondary Analysis**
Analysis population and time point description	Full Analysis Set: All patients who were randomly assigned to treatment and received any amount of olezarsen or placebo.

Descriptive statistics and estimate variability	Treatment group:	Olezarsen 80 mg	Olezarsen 50 mg	Placebo

Secondary endpoint number:	Number of subjects	22	21	23
1	TG Month 12 – 80 mg % Change from Baseline, LSM	-38.50	--	20.89
	95% CI	-58.187, -18.815	--	1.016, 40.764
2	apoC-III Month 6 – 80 mg % Change from Baseline, LSM	-66.13	--	7.57
	95% CI	-79.437, -52.823	--	-5.229, 20.359
3	apoC-III Month 12– 80 mg % Change from Baseline, LSM	-64.20	--	17.08
	95% CI	-79.408, -48.984	--	2.149, 32.009
4	≥ 40% reduction TG Month 6 – 80 mg n	9	--	1
	%	40.9	--	4.3
5	apoB-48 Month 6 – 80 mg % Change from Baseline, LSM	24.50	--	-59.46
	95% CI	-9.972, 58.973	--	-93.164, 25.765
6	Non-HDL-C Month 6 – 80 mg % Change from Baseline, LSM	-18.86	--	5.33
	95% CI	-29.952, -7.774	--	-5.345, 16.014
7	TG Month 12 – 50 mg % Change from Baseline, LSM	--	-22.92	20.89
	95% CI	--	-42.505, -3.336	1.016, 40.764
8	apoC-III Month 6 – 50 mg % Change from Baseline, LSM	--	-57.91	7.57
	95% CI	--	-71.193, -44.631	-5.229, 20.359
9	apoC-III Month 12 – 50 mg % Change from Baseline, LSM	--	-59.98	17.08
	95% CI	--	-75.163, -44.795	2.149, 32.009
10	≥ 40% reduction TG Month 6 – 50 mg	--	7	1

	n			
	%	--	33.3	4.3
11	apoB-48 Month 6 – 50 mg % Change from Baseline, LSM	--	-8.78	24.50
	95% CI	--	-42.976, 25.406	-9.972, 58.973
12	Non-HDL-C Month 6 – 50 mg % Change from Baseline, LSM	--	-12.35	5.33
	95% CI	--	-23.541, -1.163	-5.345, 16.014
13	Adjudicated pancreatitis to Week 1 to 53 – pooled olezarsen with a prior history of pancreatitis within 10 years Total 80 mg and 50 mg Mean event rate/100 patient years	6.73		66.22
	95% CI	1.612, 28.087		30.490, 143.817
14	Adjudicated pancreatitis Week 1 to 53– pooled olezarsen Total 80 mg and 50 mg Mean event rate/100 patient years	4.37		36.31
	95% CI	0.942, 20.298		14.700, 89.685
15	Adjudicated pancreatitis to Week 13 to 53 – pooled olezarsen with a prior history of pancreatitis within 10 years Total 80 mg and 50 mg Mean event rate/100 patient years	8.17		57.89
	95% CI	1.952, 34.177		24.469, 136.972
16	Adjudicated pancreatitis Week 13 to 53 – pooled olezarsen Total 80 mg and 50 mg Mean event rate/100 patient years	5.42		33.43
	95% CI	1.229, 23.897		13.250, 84.321
17	≥ 70% reduction in TG from Baseline to Month 6 – 80 mg	2	--	0

	n			
	%	9.1	--	0
18	Non-HDL-C Month 12 – 80 mg % Change from Baseline, LSM	-27.69	--	12.01
	95% CI	-41.722, -13.664	--	-2.480, 26.494
19	apoB-48 Month 12 – 80 mg % Change from Baseline, LSM	-79.15	--	-3.52
	95% CI	-118.442, -39.861	--	-53.159, 46.124
20	TG ≤ 880 mg/dL at Month 6 – 80 mg n	3	--	0
	%	14.3	--	0
21	≥ 70% reduction in TG from Baseline to Month 6 – 50 mg n	--	1	0
	%	--	4.8	0
22	Non-HDL-C Month 12 – 50 mg % Change from Baseline, LSM	--	-17.84	12.01
	95% CI	--	-32.128, -3.545	-2.480, 26.494
23	apoB-48 Month 12 – 50 mg % Change from Baseline, LSM	--	-36.41	-3.52
	95% CI	--	-77.689, 4.860	-53.159, 46.124
24	TG ≤ 880 mg/dL at Month 6 – 50 mg n	--	2	0
	%	--	10.0	0
25	Adjudicated pancreatitis Week 1 to 53 – pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment Total 80 mg and 50 mg Mean event rate/100 patient years	16.59		118.59
	95% CI	4.051, 67.948		61.226, 229.698

26	Adjudicated pancreatitis Week 13 to 53 – pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment Total 80 mg and 50 mg Mean event rate/100 patient years	21.36		106.91
	95% CI	5.233, 87.219		50.204, 227.682
27	TG ≤ 500 mg/dL at Month 6 – 80 mg n	3	--	0
	%	13.6	--	0
28	TG ≤ 500 mg/dL at Month 6 – 50 mg n	--	0	0
	%	--	0	0

Effect estimate per comparison	Secondary endpoints	Test statistic	Treatment group
Secondary endpoint number: 1	TG Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	**-59.39**
		95% CI	-90.663, -28.119
		Nominal P-value (ANCOVA)	0.0002
2	apoC-III Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-73.69
		95% CI	-94.553, -52.837
		Nominal P-value (ANCOVA)	< 0.0001
3	apoC-III Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-81.28
		95% CI	-104.656, -57.894
		Nominal P-value	< 0.0001

		(ANCOVA)	
4	≥40% reduction (placebo-controlled) TG Month 6 – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	9.27
		95% CI	1.46, 58.87
		Nominal P-value (logistic regression model)	0.0183
5	apoB-48 Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-83.97
		95% CI	-136.949, -30.982
		Nominal P-value (ANCOVA)	0.0019
6	Non-HDL-C Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-24.20
		95% CI	-40.484, -7.911
		Nominal P-value (ANCOVA)	0.0036
7	TG Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-43.81
		95% CI	-73.928, -13.692
		Nominal P-value (ANCOVA)	0.0044
8	apoC-III Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-65.48
		95% CI	-82.634, -48.320
		Nominal P-value (ANCOVA)	< 0.0001

9	apoC-III Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-77.06
		95% CI	-98.938, -55.177
		Nominal P-value (ANCOVA)	< 0.0001
10	≥ 40% reduction TG Month 6 – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	7.06
		95% CI	1.08, 46.01
		Nominal P-value (logistic regression model)	0.0409
11	apoB-48 Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-33.29
		95% CI	-82.612, 16.041
		Nominal P-value (ANCOVA)	0.1860
12	Non-HDL-C Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-17.69
		95% CI	-34.571, -0.801
		Nominal P-value (ANCOVA)	0.0401
13	Adjudicated pancreatitis to Week 1 to 53 – pooled olezarsen with a prior history of pancreatitis within 10 years	Treatment Comparison: Olezarsen vs. Placebo	Total Olezarsen 80 mg and 50 mg
		Mean Rate Ratio Olezarsen/Placebo	0.10
		95% CI	0.020, 0.506
		Nominal P-value (negative binomial)	0.0052
14	Adjudicated pancreatitis Week 1 to 53 – pooled olezarsen	Treatment Comparison: Olezarsen vs. Placebo	Total Olezarsen 80 mg and 50 mg
		Mean Rate Ratio Olezarsen/Placebo	0.12
		95% CI	0.022, 0.656

		Nominal P-value (negative binomial)	0.0144
15	Adjudicated pancreatitis to Week 13 to 53 – pooled olezarsen with a prior history of pancreatitis within 10 years	Treatment Comparison: Olezarsen vs. Placebo	Total Olezarsen 80 mg and 50 mg
		Mean Rate Ratio Olezarsen/Placebo	0.14
		95% CI	0.028, 0.709
		Nominal P-value (negative binomial)	0.0174
16	Adjudicated pancreatitis Week 13 to 53 – pooled olezarsen	Treatment Comparison: Olezarsen vs. Placebo	Total Olezarsen 80 mg and 50 mg
		Mean Rate Ratio Olezarsen/Placebo	0.16
		95% CI	0.031, 0.850
		Nominal P-value (negative binomial)	0.0314
17	≥ 70% reduction (placebo-adjusted) n TG from Baseline to Month 6 – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	4.28
		95% CI	0.31, 60.10
		Nominal P-value (logistic regression model)	0.2802
18	Non-HDL-C Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-39.70
		95% CI	-63.108, -16.292
		Nominal P-value (ANCOVA)	0.0009
19	apoB-48 Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-75.63
		95% CI	-153.195, 1.927
		Nominal P-value (ANCOVA)	0.0560
20	TG ≤ 880 mg/dL at Month 6 – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	6.90
		95% CI	0.39, 122.67
		Nominal P-value (logistic regression model)	0.1885

21	≥ 70% reduction in TG from Baseline to Month 6 – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	2.96
		95% CI	0.18, 48.98
		Nominal P-value (logistic regression model)	0.4494
22	Non-HDL-C Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-29.84
		95% CI	-53.490, -6.198
		Nominal P-value (ANCOVA)	0.0134
23	apoB-48 Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-32.90
		95% CI	-113.254, 47.459
		Nominal P-value (ANCOVA)	0.4219
24	TG ≤ 880 mg/dL at Month 6 – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	5.68
		95% CI	0.30, 108.60
		Nominal P-value (logistic regression model)	0.2487
25	Adjudicated pancreatitis Week 1 to 53 – pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment	Treatment Comparison: Olezarsen vs. Placebo	Total Olezarsen 80 mg and 50 mg
		Mean Rate Ratio Olezarsen/Placebo	0.14
		95% CI	0.029, 0.669
		Nominal P-value (negative binomial)	0.0137
26	Adjudicated pancreatitis Week 13 to 53 – pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment	Treatment Comparison: Olezarsen vs. Placebo	Total Olezarsen 80 mg and 50 mg
		Mean Rate Ratio Olezarsen/Placebo	0.20
		95% CI	0.040, 0.986
		Nominal P-value (negative binomial)	0.0480

27	TG ≤ 500 mg/dL at Month 6 – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	5.46
		95% CI	0.32, 92.54
		Nominal P-value (logistic regression model)	0.2401
28	TG ≤ 500 mg/dL at Month 6 – 50 mg n	Responder analysis (olezarsen/placebo)	Olezarsen 50 mg
		Odds ratio	1.03
		95% CI	0.03, 35.68
		Nominal P-value (logistic regression model)	0.9857

2.5.5.3. Clinical studies in special populations

There are no special studies e.g. in children, in the elderly, in pregnant or lactating women and in patients with renal or hepatic impairment which have been conducted.

The applicant provided the table below regarding the data for subjects aged 65 and older.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	41/272	8/272	0/272

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.5.5.6. Supportive study(ies)

ISIS 678354-CS8

Study population

The study included 21 sites in the United States and 7 sites in Canada.

Key inclusion criteria:

- Males and females aged ≥ 18 years at the time of informed consent
- at least 1 of the following groups (a or b):

- Hypertriglyceridemia with fasting TG ≥ 150 mg/dL (1.69 mmol/L) and < 500 mg/dL (5.65 mmol/L) with either
- Clinical diagnosis of ASCVD defined as documented coronary artery disease, cerebrovascular disease, or peripheral artery disease, or at increased risk of developing ASCVD

Key exclusion criteria:

- Diabetes with any of the following:
  - Newly diagnosed within 12 weeks of Screening;
  - HbA1c ≥ 9.5% at Screening; c. 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 hypoglycaemia within 6 months prior to Screening
- Acute coronary syndrome or stroke/transient ischemic attack within 6 months prior to Screening
- 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
- Active pancreatitis within 4 weeks prior to Screening
- Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would have rendered a patient unsuitable for inclusion:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)>3.0× upper limit of normal (ULN);
  - Total bilirubin>1.5 ULN unless due to Gilbert's syndrome;
  - Estimated glomerular filtration rate <30 mL/min/1.73 m2 (as determined by the CKD-EPI formula for creatinine clearance);
  - Urine protein/creatinine ratio (UPCR)≥ 500 mg/g.
- Uncontrolled arterial hypertension (blood pressure>180/100 mmHg) despite antihypertensive therapy

For a full list of inclusion/exclusion criteria please refer to the submitted CSR for the study ISIS 678354-CS8.

Trial Intervention

Depending on cohort, patients were randomly assigned to study drug (olezarsen or placebo) as follows:

- Cohort A: Patients were randomly assigned 3:1 to receive 50 mg olezarsen (0.5 mL) or matching volume of placebo subcutaneously once every 4 weeks from Weeks 1 to 49.
- Cohort B: Patients were randomly assigned 3:1 to receive 80 mg olezarsen (0.8 mL) or matching volume of placebo subcutaneously once every 4 weeks from Weeks 1 to 49.

There was a 53-week treatment period. During the treatment period olezarsen and matching placebo were to be administered subcutaneously as a single injection (0.5 mL for 50-mg dose, 0.8 mL for 80-

mg dose; 100 mg/mL solution in Water for Injection (WFI), stored in 2 mL stoppered glass single use vial), every 4 weeks from Week 1 to Week 49.

Primary Objective

The primary efficacy endpoint was the percent change in fasting TG from baseline at the primary analysis time point compared with the placebo group. The primary analysis time point was Month 6, which was defined as the average of Week 25 and Week 27.

Secondary Objectives

The secondary included endpoints apo-lipoprotein parameters (TG, apoC-III, VLDL-C, remnant cholesterol, total cholesterol, non-HDL-C, LDL-C, apoB, HDL-C, and apoA-1); and the incidence rate of acute pancreatitis (adjudicated by a blinded, independent committee according to Atlanta Classification [Banks et al 2013] and as outlined in the Pancreatitis Adjudication Charter) and independently adjudicated MACE. The endpoint numbers were not defined in the statistical analysis plan [SAP] and were assessed in order of hierarchy by priority for analysis. For the primary endpoint, olezarsen 80 mg treatment group was to be compared with the pooled placebo group at the 2-sided alpha level of 0.05. If the comparison was statistically significant (p-value < 0.05), then the primary endpoint would be assessed for the olezarsen 50 mg treatment group compared with pooled placebo at the same alpha level. If this subsequent comparison was statistically significant, analyses of the secondary endpoint family were to begin in order of importance.

Results

Baseline data

Demographics and baseline characteristics

Table 32 Demographics and baseline characteristics in the study ISIS 678354-CS8

Demographic/Baseline Characteristic Statistic	Placebo (N = 39)	Olezarsen 50 mg (N = 58)	Olezarsen 80 mg (N = 57)
Age at Informed Consent (years)			
Mean (SD, SEM)	63.3 (9.52, 1.53)	62.3 (10.15, 1.33)	60.4 (10.77, 1.43)
Median (P25, P75)	63.0 (58.0, 71.0)	63.0 (54.0, 71.0)	60.0 (54.0, 69.0)
Minimum, Maximum	46, 83	38, 83	35, 83
Age Category (years), n (%)			
< 65	23 (59.0)	33 (56.9)	34 (59.6)
≥ 65	16 (41.0)	25 (43.1)	23 (40.4)
Gender, n (%)			
Female	24 (61.5)	24 (41.4)	17 (29.8)
Male	15 (38.5)	34 (58.6)	40 (70.2)
Ethnicity, n (%)			
Hispanic or Latino	13 (33.3)	21 (36.2)	23 (40.4)
Not Hispanic or Latino	26 (66.7)	37 (63.8)	34 (59.6)
Race, n (%)			
White	34 (87.2)	54 (93.1)	52 (91.2)
Black	5 (12.8)	3 (5.2)	5 (8.8)
Asian	0	1 (1.7)	0
Country, n (%)[a]			
United States	35 (89.7)	55 (94.8)	56 (98.2)
Canada	4 (10.3)	3 (5.2)	1 (1.8)
BMI (kg/m²)			
Mean (SD, SEM)	34.60 (6.303, 1.009)	34.51 (6.918, 0.908)	32.69 (6.012, 0.796)
Median (P25, P75)	33.02 (30.68, 37.90)	32.93 (29.72, 38.42)	32.43 (27.61, 36.64)
Minimum, Maximum	24.1, 57.7	24.7, 56.0	22.8, 50.3
HbA1c (%)			
Mean (SD, SEM)	6.67 (0.889, 0.142)	6.58 (0.943, 0.124)	6.52 (1.068, 0.141)
Median (P25, P75)	6.60 (6.00, 7.30)	6.30 (5.90, 7.30)	6.40 (5.80, 7.00)
Minimum, Maximum	4.2, 8.9	5.2, 9.1	4.8, 10.0

Source: Table 14.1.4.1
Note: Percentages were based on the number of Full Analysis Set patients in each treatment group or overall. The Baseline for body weight, BMI, and HbA1c was defined as the last non-missing assessment prior to the first dose of study drug.
[a] Ad hoc information provided separately from the source table noted above.
Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation; SEM = standard error of the mean

Outcomes and estimation

The primary efficacy endpoint was the percent change in fasting TG from Baseline at the primary analysis time point compared with the placebo group. The secondary endpoints included apo-lipoprotein parameters (TG, apoC-III, VLDL-C, remnant cholesterol, total cholesterol, non-HDL-C, LDL-C, apoB, HDL-C, and apoA-1); and the incidence rate of acute pancreatitis (adjudicated by a blinded, independent committee according to Atlanta Classification [Banks et al 2013] and as outlined in the Pancreatitis Adjudication Charter) and independently adjudicated MACE. Assessments were performed

at the frequencies noted in the Schedule of Procedures in the study protocol. The primary analysis time point was Month 6, which was defined as the average of Week 25 and Week 27.

Table 33. Summary of efficacy for trial 678354-CS8.

Primary and secondary endpoint results				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set: All patients who were randomly assigned to treatment and received any amount of olezarsen or placebo.			
Descriptive statistics and estimate variability Primary Endpoints	Treatment group	Olezarsen 80 mg	Olezarsen 50 mg	Placebo
	Number of subjects	57	58	39
	TG Month 6 – 80 mg % Change from Baseline, least squares mean (LSM)	-60.92	--	-7.77
	95% CI	-67.11, -54.73	--	-15.34, -0.21
	TG Month 6 – 50 mg % Change from Baseline, LSM	--	-57.05	-7.77
	95% CI	--	-63.19, -50.92	-15.34, -0.21
Effect estimate per comparison	Primary endpoints	Test statistic	Treatment group	
	TG Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg	
		Placebo-adjusted % Change from Baseline LSM	-53.15	
		95% CI	-62.92, -43.38	
		P-value (analysis of covariance [ANCOVA])	<0.0001	
	TG Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg	
		Placebo-adjusted % Change from Baseline LSM	-49.28	
		95% CI	-59.02, -39.54	
		P-value (ANCOVA)	<0.0001	
Notes	Overall, Study ISIS 678354-CS8 shows a meaningful benefit of olezarsen on TG level decreases for the treatment of patients with hypertriglyceridemia, established or increased risk of ASCVD, and/or sHTG. The primary efficacy endpoint, percent change in fasting TG from Baseline at Month 6 (average of Week 25 and Week 27) in both the olezarsen 80 mg and 50 mg groups compared with the pooled placebo group, was met in this study: patients in the olezarsen 80 mg and 50 mg groups achieved placebo-adjusted mean percent decreases in TG levels from Baseline of			

	53.15% and 49.28% at Month 6, respectively. These results were statistically significant (p-value < 0.0001) for both olezarsen treatment groups.			
Analysis description	**Secondary Analysis**			
Analysis population and time point description	Full Analysis Set: All patients who were randomly assigned to treatment and received any amount of olezarsen or placebo.			
Descriptive statistics and estimate variability	Treatment group:	Olezarsen 80 mg	Olezarsen 50 mg	Placebo
Secondary endpoint number:	Number of subjects	57	58	39
1	TG Month 12 – 80 mg % Change from Baseline, LSM	-60.39	--	-5.59
	95% CI	-66.51, -54.27	--	-13.09, 1.90
2	TG Month 12 – 50 mg % Change from Baseline, LSM	--	-51.67	-5.59
	95% CI	--	-57.74, -45.60	-13.09, 1.90
3	apoC-III Month 6 – 80 mg % Change from Baseline, LSM	-78.72	--	-5.47
	95% CI	-87.79, -69.65	--	-16.46, 5.51
4	apoC-III Month 12 – 80 mg % Change from Baseline, LSM	-83.78	--	-12.40
	95% CI	-93.22, -74.34	--	-24.02, -0.77
5	apoC-III Month 6 – 50 mg % Change from Baseline, LSM	--	-69.63	-5.47
	95% CI	--	-79.56, -59.71	-16.46, 5.51
6	apoC-III Month 12 – 50 mg % Change from Baseline, LSM	--	-69.09	-12.40
	95% CI	--	-79.42, -58.76	-24.02, -0.77

7	TG < 150 mg/dL Month 6 subset with Baseline TG < 500 mg/dL – 80 mg n	42	--	4
	%	84.0	--	11.4
8	TG < 150 mg/dL Month 12 subset with Baseline TG < 500 mg/dL – 80 mg n	41	--	2
	%	82.0	--	5.7
9	VLDL-C Mont h 6 – 80 mg % Change from Baseline, LSM	-59.46	--	-9.74
	95% CI	-68.79, -50.13	--	-20.65, 1.17
10	VLDL-C Mont h 12 – 80 mg % Change from Baseline, LSM	-66.67	--	-14.90
	95% CI	-74.47, -58.87	--	-23.97, -5.82
11	VLDL-C Mont h 6 – 50 mg % Change from Baseline, LSM	--	-55.93	-9.74
	95% CI	--	-65.65, -46.22	-20.65, 1.17
12	VLDL-C Mont h 12 – 50 mg % Change from Baseline, LSM	--	-58.00	-14.90
	95% CI	--	-66.11, -49.88	-23.97, -5.82

13	Non-HDL-C Month 6 – 80 mg % Change from Baseline, LSM	-19.79	--	3.28
	95% CI	-28.72, -10.85	--	-7.04, 13.61
14	Non-HDL-C Month 12 – 80 mg % Change from Baseline, LSM	-26.57	--	-2.55
	95% CI	-34.59, -18.55	--	-11.91, 6.81
15	Non-HDL-C Month 6 – 50 mg % Change from Baseline, LSM	--	-22.11	3.28
	95% CI	--	-31.33, -12.89	-7.04, 13.61
16	Non-HDL-C Month 12 – 50 mg % Change from Baseline, LSM	--	-20.00	-2.55
	95% CI	--	-28.23, -11.76	-11.91, 6.81
17	TG < 150 mg/dL Month 6 subset with Baseline TG < 500 mg/dL – 50 mg N	--	42	4
	%	--	79.2	11.4
18	TG < 150 mg/dL Month 12 subset with Baseline TG < 500 mg/dL – 50 mg N	--	37	2
	%	--	69.8	5.7
19	HDL-C Month 6 – 80 mg % Change from Baseline, LSM	48.01	--	8.38
	95% CI	37.18, 58.83	--	-3.70, 20.46
20	HDL-C Month 12 – 80 mg % Change from Baseline, LSM	57.43	--	10.53
	95% CI	46.32, 68.53	--	-1.87, 22.94
21	HDL-C Month 6 – 50 mg % Change from Baseline, LSM	--	48.02	8.38

	95% CI	--	37.00, 59.04	-3.70, 20.46
22	HDL-C Month 12 – 50 mg % Change from Baseline, LSM	--	54.20	10.53
	95% CI	--	42.94, 65.47	-1.87, 22.94
23	Remnant-C Month 6 – 80 mg % Change from Baseline, LSM	-59.59	--	-9.46
	95% CI	-68.96, -50.22	--	-20.39, 1.47
24	Remnant-C Month 12 – 80 mg % Change from Baseline, LSM	-66.90	--	-14.83
	95% CI	-74.63, -59.17	--	-23.85, -5.82
25	Remnant-C Month 6 – 50 mg % Change from Baseline, LSM	--	-55.98	-9.46
	95% CI	--	-65.73, -46.23	-20.39, 1.47
26	Remnant-C Month 12 – 50 mg % Change from Baseline, LSM	--	-58.17	-14.83
	95% CI	--	-66.20, -50.13	-23.85, -5.82
27	apoB Month 6 = 80 mg % Change from Baseline, LSM	-11.67	--	6.82
	95% CI	-18.80, -4.53	--	-1.44, 15.07
28	apoB Month 12 – 80 mg % Change from Baseline, LSM	-18.53	--	0.68
	95% CI	-25.12, -11.93	--	-7.09, 8.44
29	apoB Month 6 – 50 mg % Change from Baseline, LSM	--	-11.42	6.82
	95% CI	--	-18.80, -4.03	-1.44, 15.07
30	apoB Month 12 – 50 mg % Change from Baseline, LSM	--	-11.67	0.68
	95% CI	--	-18.45, -4.90	-7.09, 8.44

31	apoA-1 Month 6 – 80 mg % Change from Baseline, LSM	14.91	--	2.84
	95% CI	10.49, 19.32	--	-2.19, 7.87
32	apoA-1 Month 12 – 80 mg % Change from Baseline, LSM	15.46	--	0.81
	95% CI	11.15, 19.76	--	-4.11, 5.72
33	apoA-1 Month 6 – 50 mg % Change from Baseline, LSM	--	17.37	2.84
	95% CI	--	12.82, 21.93	-2.19, 7.87
34	apoA-1 Month 12 – 50 mg % Change from Baseline, LSM	--	16.37	0.81
	95% CI	--	11.97, 20.78	-4.11, 5.72
35	LDL-C Month 6 – 80 mg % Change from Baseline, LSM	32.74	--	40.46
	95% CI	19.35, 46.14	--	25.11, 55.80
36	LDL-C Month 12 – 80 mg % Change from Baseline, LSM	27.27	--	35.08
	95% CI	15.28, 39.26	--	21.09, 49.08
37	LDL-C Month 6 – 50 mg % Change from Baseline, LSM	--	30.61	40.46
	95% CI	--	16.44, 44.77	25.11, 55.80
38	LDL-C Month 12 – 50 mg % Change from Baseline, LSM	--	32.99	35.08
	95% CI	--	20.52, 45.46	21.09, 49.08
39	Total Chol Month 6 - 80 mg % Change from Baseline, LSM	-6.48	--	2.99
	95% CI	-13.31, 0.35	--	-4.94, 10.92
40	Total Chol Month 12 -	-10.8	--	-2.15

	80 mg % Change from Baseline, LSM			
	95% CI	-16.87, -4.72	--	-9.25, 4.95
41	Total Chol Month 6 - 50 mg % Change from Baseline, LSM	--	-6.78	2.99
	95% CI	--	-13.86, 0.30	-4.94, 10.92
42	Total Chol Month 12 - 50 mg % Change from Baseline, LSM	--	-6.08	-2.15
	95% CI	--	-12.35, 0.18	-9.25, 4.95
43	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 6 – 80 mg n	7	--	3
	%	100.0	--	75.0
44	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 12 – 80 mg n	7	--	3
	%	100.0	--	75.0
45	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 6 – 50 mg n	--	4	3
	%	--	80.0	75.0
46	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 12 – 50 mg n	--	5	3
	%	--	100.0	75.0
47	Adjudicated pancreatitis– pooled olezarsen Mean event rate/100 patient years	Could not be evaluated because no patients in any treatment group had an adjudicated acute pancreatitis event during the treatment period.		--

	95% CI	--	--
48	Adjudicated pancreatitis– pooled olezarsen subset with ≥ 2 events in 5 years prior to enrolment Mean event rate/100 patient years	Could not be evaluated because no patients in any treatment group had an adjudicated acute pancreatitis event during the treatment period.	--
	95% CI	--	--

Effect estimate per comparison	Secondary endpoints	Test statistic	Treatment group
Secondary endpoint number: 1	TG Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-54.80
		95% CI	-64.46, -45.13
		P-value (analysis of covariance [ANCOVA])	< 0.0001
2	TG Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-46.07
		95% CI	-55.71, -36.43
		P-value (ANCOVA)	< 0.0001
3	apoC-III Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-73.25
		95% CI	-83.94, -62.55
		P-value (ANCOVA)	< 0.0001
4	apoC-III Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-71.39
		95% CI	-82.62, -60.15
		P-value	< 0.0001

		(ANCOVA)	
5	apoC-III Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-64.16
		95% CI	-74.69, -53.63
		P-value (ANCOVA)	< 0.0001
6	apoC-III Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-56.70
		95% CI	-67.73, -45.66
		P-value (ANCOVA)	< 0.0001
7	TG < 150 mg/dL Month 6 subset with Baseline TG < 500 mg/dL – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	62.59
		95% CI	15.48, 253.07
		P-value (logistic regression model)	< 0.0001
8	TG < 150 mg/dL Month 12 subset with Baseline TG < 500 mg/dL – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	80.89
		95% CI	15.95, 410.36
		P-value (logistic regression model)	< 0.0001
9	VLDL-C Mont h 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-49.72
		95% CI	-60.26, -39.18
		P-value (ANCOVA)	< 0.0001
10	VLDL-C Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-51.77
		95% CI	-60.60, -42.95

		P-value (ANCOVA)	< 0.0001
11	VLDL-C Mont h 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-46.19
		95% CI	-56.69, -35.69
		P-value (ANCOVA)	< 0.0001
12	VLDL-C Mont h 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-43.10
		95% CI	-51.88, -34.32
		P-value (ANCOVA)	< 0.0001
13	Non-HDL-C Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-23.07
		95% CI	-34.02, -12.11
		P-value (ANCOVA)	< 0.0001
14	Non-HDL-C Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-24.02
		95% CI	-33.98, -14.06
		P-value (ANCOVA)	< 0.0001
15	Non-HDL-C Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-25.39
		95% CI	-36.33, -14.46
		P-value (ANCOVA)	< 0.0001

16	Non-HDL-C Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-17.45
		95% CI	-27.37, -7.52
		P-value (ANCOVA)	0.0006
17	TG < 150 mg/dL Month 6 subset with Baseline TG < 500 mg/dL – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	37.51
		95% CI	10.14, 138.81
		P-value (logistic regression model)	< 0.0001
18	TG < 150 mg/dL Month 12 subset with Baseline TG < 500 mg/dL – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	38.46
		95% CI	8.13, 181.95
		P-value (logistic regression model)	< 0.0001
19	HDL-C Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	39.63
		95% CI	26.61, 52.65
		P-value (ANCOVA)	< 0.0001
20	HDL-C Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	46.89
		95% CI	33.52, 60.27
		P-value (ANCOVA)	< 0.0001
21	HDL-C Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	39.64
		95% CI	26.71, 52.57
		P-value	< 0.0001

		(ANCOVA)	
22	HDL-C Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	43.67
		95% CI	30.39, 56.95
		P-value (ANCOVA)	< 0.0001
23	Remnant-C Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-50.13
		95% CI	-60.71, -39.56
		P-value (ANCOVA)	< 0.0001
24	Remnant-C Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-52.07
		95% CI	-60.82, -43.31
		P-value (ANCOVA)	< 0.0001
25	Remnant-C Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-46.52
		95% CI	-57.06, -35.99
		P-value (ANCOVA)	< 0.0001
26	Remnant-C Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-43.33
		95% CI	-52.04, -34.62
		P-value (ANCOVA)	< 0.0001

27	apoB Month 6 - 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-18.48
		95% CI	-27.36, -9.61
		P-value (ANCOVA)	< 0.0001
28	apoB Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-19.20
		95% CI	-27.58, -10.82
		P-value (ANCOVA)	< 0.0001
29	apoB Month 6 - 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-18.24
		95% CI	-27.11, -9.36
		P-value (ANCOVA)	< 0.0001
30	apoB Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-12.35
		95% CI	-20.70, -3.99
		P-value (ANCOVA)	0.0038
31	apoA-1 Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	12.07
		95% CI	6.62, 17.52
		P-value (ANCOVA)	< 0.0001
32	apoA-1 Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg

		Placebo-adjusted % Change from Baseline LSM	14.65
		95% CI	9.32, 19.99
		P-value (ANCOVA)	< 0.0001
33	apoA-1 Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	14.53
		95% CI	9.11, 19.96
		P-value (ANCOVA)	< 0.0001
34	apoA-1 Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	15.57
		95% CI	10.26, 20.87
		P-value (ANCOVA)	< 0.0001
35	LDL-C Month 6 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-7.71
		95% CI	-24.16, 8.73
		P-value (ANCOVA)	0.3579
36	LDL-C Month 12 – 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-7.81
		95% CI	-22.90, 7.27
		Nominal P-value (ANCOVA)	0.3099
37	LDL-C Month 6 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg

		Placebo-adjusted % Change from Baseline LSM	-9.85
		95% CI	-26.33, 6.63
		Nominal P-value (ANCOVA)	0.2413
38	LDL-C Month 12 – 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-2.09
		95% CI	-17.15, 12.96
		Nominal P-value (ANCOVA)	0.7850
39	Total Chol Month 6 - 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-9.47
		95% CI	-17.97, -0.97
		Nominal P-value (ANCOVA)	0.0289
40	Total Chol Month 12 - 80 mg	Difference (olezarsen-placebo)	Olezarsen 80 mg
		Placebo-adjusted % Change from Baseline LSM	-8.65
		95% CI	-16.27, -1.02
		Nominal P-value (ANCOVA)	0.0264
41	Total Chol Month 6 - 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-9.77
		95% CI	-18.25, -1.30
		Nominal P-value (ANCOVA)	0.0238

42	Total Chol Month 12 - 50 mg	Difference (olezarsen-placebo)	Olezarsen 50 mg
		Placebo-adjusted % Change from Baseline LSM	-3.93
		95% CI	-11.53, 3.67
		Nominal P-value (ANCOVA)	0.3107
43	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 6 – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	5.74
		95% CI	0.17, 190.69
		Nominal P-value (logistic regression model)	0.3281
44	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 12 – 80 mg	Responder analysis	Olezarsen 80 mg
		Odds ratio (olezarsen/placebo)	7.30
		95% CI	0.14, 388.49
		Nominal P-value (logistic regression model)	0.3271
45	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 6 – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	4.46
		95% CI	0.12, 169.94
		Nominal P-value (logistic regression model)	0.4212
46	TG < 500 mg/dL Month 6 subset with Baseline TG ≥ 500 mg/dL Month 12 – 50 mg	Responder analysis	Olezarsen 50 mg
		Odds ratio (olezarsen/placebo)	4.49
		95% CI	0.07, 270.10
		Nominal P-value (logistic regression model)	0.4722
47	Adjudicated pancreatitis– pooled olezarsen	Could not be evaluated because no patients in any treatment group had an adjudicated acute pancreatitis event during the treatment period.	--

48	Adjudicated pancreatitis– pooled olezarsen subset with ≥ 2 events in 5 years prior to enrollment	Could not be evaluated because no patients in any treatment group had an adjudicated acute pancreatitis event during the treatment period.	--

2.5.6. Discussion on clinical efficacy

The applicant is requesting a marketing authorization for Tryngolza (olezarsen) administered as subcutaneous injection 80 mg in patients with familial chylomicronemia syndrome. The following indication was initially proposed:

"*Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of familial chylomicronemia syndrome (FCS) to reduce triglycerides and the rate of acute pancreatitis events*".

The efficacy data are currently based on the pivotal ISIS 678354-CS3 study, which was randomized, double-blind, placebo-controlled, phase 3 trial in patients with Familial Chylomicronemia Syndrome (FCS). The applicant submitted also a supportive study ISIS 678354-CS8, which was 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. There are two ongoing studies with olezarsen, one of them is the ISIS 678354CS13 study – an extension of the pivotal study ISIS 678354-CS3 study, which is an open label study in patients with FCS. The other one is an open-label safety Study of olezarsen (AKCEA-APOCIII-LRXa), administered subcutaneously to patients with FCS previously treated with volanesorsen. There are only interim analyses submitted by the applicant in the application. The latest or final clinical efficacy data from both open label studies has been provided by the applicant Despite the observed fluctuations in the fasting Tg levels observed, the long-term decrease in TG level could be maintained in comparison with the that one prior the treatment initiation.

Design and conduct of clinical studies

Design and conduct of the clinical study ISIS 678354 CS3

The pivotal 678354-CS3 trial was a multicentre, randomized, double-blind, placebo-controlled, 53-week study testing olezarsen at the dose of 50 mg or 80 mg administered once every 4 weeks. The study design included a first screening period (approximately 4-week, but no more than 8-week) comprehensive of at least a 2-week diet stabilization/run in period for patients not already on a stable diet (≤20 g fat per day), and an approximately 2-week qualification period. Patients then entered a 53-week treatment period, and a 13-week post treatment evaluation period or enrolment into the open-label extension (OLE) Study ISIS 678354 CS13, thus offering the possibility to evaluate treatment at relevant clinical time points for a chronically administrated therapy, and effect maintenance in the long-term. The pivotal study ISIS 678354CS3 was conducted in the targeted population of FCS (type 1 Hyperlipoproteinemia) patients with history of pancreatitis defined as recorded acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis within 10 years prior to Screening. Recruitment of patients without prior history of pancreatitis was allowed with a capping at 35% of the planned population, as part of an enrichment strategy to reasonably optimise clinical event accumulation. The recruitment of patients was done at 29 sites including 9 sites in the United States (US), 3 sites in Canada, 16 sites in the European Union (EU) countries, and 1 site in the United Kingdom (UK). The patient population is considered to be adequately selected according to the inclusion/exclusion criteria. Baseline demographics are considered slightly disbalanced between treatment and control groups with

regard to the acute pancreatitis, the estimated mean number of events for the last was almost as much as twice higher in the placebo group compared to both olezarsen groups. Overall, the study population appears to reflect the intended indication. Overall, based on the patients' medical history approximately 30% (5/18) of all cases of volanesorsen discontinuation were related to the adverse events. The biggest special population was presented by patients with hepatic impairment and patients older than 65 years. The patients with renal impairment were presented with about 1.2-2% of the total population.

One of the main inclusion criteria was the fasting TG ≥ 880 mg/dL (10 mmol/L) at Screening and the confirmed diagnosis of FCS. Based on the main inclusion criteria the patients' population consisted of patients with documented genetically confirmed familial chylomicronemia syndrome (FCS) (i.e. loss-of-function mutations in type 1-causing genes such as LPL, GPIHBP1, APOA5, APOC2, GPD1, or LMF1). This was not reflected in the initial proposed indication, but the applicant agreed to revise the indication to the treatment of patients with genetically confirmed FCS in line with the request from the CHMP. Based on the inclusion criteria at enrolment and during the study, patients had to follow a diet comprising of ≤ 20 g fat per day. The adjunction to diet is principally covered by the proposed indication. Olezarsen was used on top of lipid lowering therapy from the patients' enrolment into the study and continued after first dose of study's drug without changing the treatment policy. It is considered that lipid lowering therapy is of relevance to prescribers in the identification of the possible use of the drug within the current therapeutic practice. However, it is unlikely to make influence on therapeutic effect of olezarsen in patients with FCS due the origin of the disease. Therefore, it is considered that information about lipid lowering therapy could be a part of 5.1 section of SmPC, rather than included in the indication text.

The patients' population in the Balance study (trial 678354-CS3) is not considered enriched by patients with diabetes or hypertension. It is acknowledged that those patients were on stable dose regimen of anti-diabetic or anti-hypertensive therapy during the study. Moreover, the risk of acute pancreatitis increases relative to the elevation in serum triglycerides, with the incidence of acute pancreatitis increasing 3% to 4% for every 100 mg/dL incremental increase in triglycerides level (Murphy 2013; Rashid 2016). A TG level > 880 mg/dL has been shown to be associated with persistent chylomicronemia; therefore, the risk of acute pancreatitis is greater compared with lower TG levels for which chylomicrons are not consistently observed (Sanchez et al. 2021). This risk further increases when TG levels are > 2000 mg/dL (Berglund et al. 2012; Toth et al. 2014). Considering that the baseline level of fasting TG in patients enrolled in the Balance study was more than 2000 mg/dL, the overall population is considered at high risk of acute pancreatitis regardless of prior history of acute pancreatitis. The CHMP considers that the indication of olezarsen for a broader patients' population regardless of prior history of acute pancreatitis is justified.

Overall, as an indication should define the target disease or condition, it is considered that the target condition in case of treatment effect of olezarsen is a genetically confirmed FCS, not the reduction of triglycerides and the rate of acute pancreatitis events. Information on the reduction of triglycerides and the acute pancreatitis event rate is proposed to be included in section 5.1 of SmPC. The indication has been revised by the applicant and "reduce triglycerides and the rate of acute pancreatitis events" has been removed from the statement of the indication. However, a reference to the trial results with respect to the reduction of triglycerides and the rate of acute pancreatitis was maintained in section 4.1 of the SmPC and this was not supported by the CHMP. The CHMP position was that these results can be included into section 5.1 of SmPC, if clinically relevant and statistically significant, but should not be a part of the indication statement and should therefore be deleted from section 4.1. The applicant agreed with the CHMP position, and the text of the indication statement was updated accordingly.

Overall, it is considered that the design of the study was adequate and the placebo on top of standard care (i.e. extremely restrictive diet devoid of nearly all dietary fat with or without lipid lowering agents) was an acceptable comparator.

Patients were randomized to receive 50 mg olezarsen (0.5 ml), 80 mg olezarsen (0.8 ml) or matching volume of placebo as subcutaneously injection once every 4 weeks for Weeks 1 to 49. Patients had to follow a diet comprising ≤ 20 g fat per day and were allowed to continue lipid lowering therapy such as statins, omega-3 fatty acids (prescription and OTC), fibrates, or other lipid-lowering medications. Olezarsen dose selection was based upon pre-clinical and clinical considerations. It appears that the PK/PD analysis was misinterpreted leading to selection of a suboptimal dose with respect to the assumptions. The applicant is clarified the discrepancy between available data and their interpretation and eventually explain the underperformance of the selected dose with respect to expectations. It is acknowledged that the safety profile of the proposed dose is supported by a >20-fold non-clinical safety margin below NOAEL, and by data from other members of the class of GalNAc3-conjugated ASOs. Considering the favourable safety profile of olezarsen the patients who either cannot tolerate high dose of volanesorsen or have platelet count from < 140 × 109/L to < 100 × 109/L (volanesorsen is contraindicated to be used in this patient population due to significant safety concerns) could benefit from the treatment with olezarsen 80 mg. Even though the dose of olezarsen is lower than it could be based on the NOAEL study results in monkeys, decrease in fasting TG and apoC-III levels at Month 6 and Month 12 and later in the observation phase (+2+3 year), demonstrated that the number of acute pancreatitis events could be significantly decreased compared with placebo.

The sample size calculation assumed that an expected standard deviation of the percent change from baseline in TG was approximately 46%. With 14 patients in each olezarsen treatment group and 14 patients in the pooled placebo group, it was estimated a 90% power to detect a 60% difference between each olezarsen treatment group and pooled placebo group at an alpha level of 0.05 (2-sided), assuming a 60% reduction in TGs in olezarsen-treated patients and no change in placebo-treated patients. Baseline randomization was stratified by prior history of pancreatitis within 10 years prior to screening vs. no history of pancreatitis or no history within 10 years prior to screening, and previous treatment with volanesorsen (Waylivra). To control the overall Type I error rate at 0.05 across the primary endpoints and secondary endpoints for the final analysis, the gatekeeping testing strategy was applied to the primary endpoint family and secondary endpoint family. The hierarchical testing procedure was utilized within the primary endpoint family and secondary endpoint family. For the primary endpoint family, the 2 treatment arms were compared against pooled placebo using the hierarchical testing procedure, in which the 80 mg olezarsen treatment group was compared to the pooled placebo at the 2-sided alpha level of 0.05. In case of statistical significance for the 80 mg olezarsen group ($p < 0.05$), then the olezarsen 50-mg treatment group is compared against the pooled placebo at the alpha level of 0.05. Then the same strategy was applied for the 50-mg treatment group against pooled placebo and all secondary endpoints. Testing of secondary endpoint family could be performed only if the comparison of the primary endpoint is statistically significant ($p < 0.05$) for both 80-mg and 50-mg olezarsen treatment.

Primary endpoint. In the Study ISIS 678354 CS3 the percent change from Baseline to the primary analysis time point in fasting TG was compared between each olezarsen treatment group versus pooled placebo using an analysis of covariates (ANCOVA) model in the Full Analysis Set. The ANCOVA model included the effects of treatment (olezarsen 80 mg, olezarsen 50 mg, or placebo), 2 randomization stratification factors (history of pancreatitis and previous treatment with volanesorsen), and log transformed Baseline TG. The 95% confidence interval (CI) of the treatment differences was calculated using the robust variance estimator based on the Bell and McCaffrey method to account for potential heterogeneity in variance. Methods similar to that of the primary analysis (i.e., ANCOVA model in the Full Analysis Set) were used to analyse secondary endpoints for the percent change in

fasting lipid and apolipoprotein parameters (i.e., TG, apoC-III, apoB 48, non-HDL C) from Baseline to Month 6 and/or Month 12. In addition, the incidence rate of acute pancreatitis (adjudicated by a blinded, independent committee according to the Atlanta Classification) was reported during both the whole study period (from Week 1 to Week 53) and in the post-treatment phase (Week 13 to Week 53). The additional exploratory endpoints for this study included a comparison of MACE rates between the olezarsen 80 mg group or the olezarsen 50 mg group and the placebo group, TG threshold response rates and TG percent reductions between olezarsen treatment groups (olezarsen 80 mg group and olezarsen 50 mg group) and placebo, and changes in broader healthcare utilization and patient-reported outcomes.

To assess the robustness of the primary analysis the Sensitivity Analysis 3 was performed using different imputation approaches (pattern mixture model). Overall, the proposal for missing data imputation using different assumptions for missingness, including also a tipping point analysis, is considered appropriate; however, a jump to reference approach should be applied also to patients who received prohibited medications since this ICE constitutes a failure of treatment to manage the patient's disease. This was raised in the LoQ. In its response, the applicant stated that no patients in the olezarsen 50 mg group received additional prohibited lipid-lowering medication. Only one patient in the olezarsen 80 mg group received prohibited lipid-lowering medication (Tricor) on Day 361 for pancreatitis. This additional medication is not expected to affect the efficacy analyses because the Month 12 lipid data for this patient were based on measurements from Day 351. Data collected after Day 351 for this patient fall outside analysis windows and were therefore not included in any efficacy analyses. Therefore, the applicant concludes a jump to reference approach is not applicable. This is considered acceptable by the CHMP.

The applicant was asked to provide information about frequency and timing for discontinuation of therapy and use of prohibited medication for each arm together with corresponding reasons to evaluate their impact on the primary analysis as well as secondary analyses. The applicant has provided the requested data. The revision of the newly submitted information does not raise any further concern.

In general, the proposed statistical tests, estimation methods, and multiplicity adjustments are considered acceptable. The proposed Statistical Analysis Plan adequately supported the testing of the hypothesis. No post-hoc amendments of the statistical analysis plan have an impact on the overall validity of the clinical trial results. The proposed assumptions for power and sample size calculations are acceptable. The applicant has provided only high-level description of sample size estimation without SAS (or R) code in the statistical analysis plan. However, methods of sample size estimation along with clinical trial simulations to support the proposed sample size of the pivotal clinical trial are needed and were requested to the applicant in the LoQ. In its response, The applicant has provided an explanation that nQuery was used to estimate sample size and that A simulation was performed using the percent change in TG at Month 6 data from the Waylivra pivotal FCS study. The applicant also pointed out that the data were analyzed using an ANCOVA model with the treatment group as a fixed effect and log-transformed baseline values as a covariate. The simulation study demonstrated a power exceeding 90%. The issue is partly resolved and will not be pursued further. Moreover, the applicant was also requested to conduct a supplementary analysis of primary endpoint with a mixed models for repeated measures. The applicant performed a mixed model for repeated measures for the primary endpoint the percent change in triglycerides from baseline to the primary analysis time point (Month 6). The analysis supports the primary analysis.

The secondary efficacy endpoints based on the proportion of patients who achieve a pre-defined cut-off value were analysed similarly to the primary endpoint using the same multiple imputation method for missing data, and the ICEs were handled using the treatment policy strategy. In addition, as sensitivity

analysis, all patients with missing data and who discontinued study treatment were counted as non-responders. This is considered conservative and is acceptable.

The rate of major protocol deviations was quite high in the pivotal trial (47%). The most common major protocol deviations were related to improper informed consent procedures (31.8% in the 80 mg olezarsen group, 19% in the 50 mg olezarsen group and 17.4% in the placebo). It is noted that for many of these deviations, an action was taken to retrain or remind the site personnel to ensure that updated ICF forms were signed in a timely manner. Additional reasons for major protocol deviations included errors in study procedures, missing visits and drug errors, all of them apparently equally distributed across groups. Eleven patients experienced ≥ 3 major protocol deviations (6 patients in the olezarsen 80 mg group, 2 patients in the olezarsen 50 mg group, and 3 patients in the placebo group). Two patients experienced ≥ 10 major deviations during the study. Both patients completed treatment in the study and are included in all relevant analysis populations. The outcome of the study is reported not to have been affected by the protocol deviations

Efficacy data and additional analyses

The application is based on the final analysis (FA) of the CS3 trial (DCO: 23-JUL-2023). A total of 144 patients were enrolled, with 78 (54%) excluded for screen-failures and 66 randomised to treatment. At the time of the FA, most patients had completed study drug treatment (85.4% in the olezarsen 80 mg group, 90% in the olezarsen 50 mg group and 95.7% for the placebo) and enrolled in the OLE study (ISIS 678354-CS13), including 72.7% in the olezarsen 80 mg group, 81.0% of patients in the olezarsen 50 mg group, and 82.6% for the placebo group. Drug discontinuation was 13.6% (3/22 patients) in the 80 mg olezarsen arm, mainly related to AEs and SAEs (9.1%; 2/22 patients) or voluntary withdrawal (4.5%, 1/22 patients). In the 50 mg olezarsen group, the rate of drug discontinuation was lower (9.5%; 2/21 patients) and equally attributed to adverse events (4.8%; 1/21 patients) or voluntary withdrawal (4.8%; 1/21 patients), while none of the patients assigned to placebo (n=23) discontinued treatment.

The study population, aged between 43 and 47 years in median across studies, can be considered representative of FCS patients at high risk of pancreatitis, having genetically determined FCS (100% of the population with 55 out of 66 patients harboring mutations in the LPL gene), severe HTG despite diet restriction and pharmacological treatment (2629.5 mg/dl in mean in the FAS), and prior history of pancreatitis in the majority of cases (80%). Patients were all on standard diet restriction, mostly on concomitant treatment with other lipid-lowering agents including statins (24.2%), omega-3 fatty acids (37.9%) and fibrates (45.5%) or ezetimibe and PCK91 (9.1%). Upon request, the applicant clarified that more than half of the population (around 66%) was on lipid lowering agents in addition to diet restriction. The efficacy subgroup analysis by use of lipid-lowering agents was provided. No specific differences from the total population were observed. Diabetics with no restrictions based on HbA1c levels (27.1% of the FAS) were also included. Baseline patient and disease characteristics were overall balanced among treatment arms.

The primary endpoint – a change in fasting TG level compared to placebo at Month 6 – is considered a clinically relevant endpoint. Mainly based on clinical experience, the opinion of experts is to recommend maintaining plasma TG levels below 500-1.000 mg/dL to prevent pancreatitis (Okazaki H et al, 2021; Burnett JR et al, 1993; Berglund L et al, 2012; Ad-Hoc Expert Advisory Group, EMA/180717/2019 CHMP AR, 2019). The treatment goal of chylomicronemia is to lower plasma TG levels enough to reduce the risk of pancreatitis. Approximately 60 patients were planned to be enrolled in this trial to account for potential early dropouts and to facilitate some general safety evaluations. However, a total of 66 patients were enrolled in the pivotal study. Based on the description of estimand for the primary endpoint, it is considered that it was adequately defined, clinically relevant and acceptable. However, as a general principle (EMA/CHMP/748108/2013), demonstration of clinical

benefit also requires support from clinically relevant data on morbidity and mortality associated with the disturbed lipid levels. In the setting of FCS treatment, the clinical relevance of TG reduction should be interpreted in view of a prophylactic action against the occurrence of acute pancreatitis, which represents the primary therapeutic goal. According to the applicant, based upon prior clinical trial experience with FCS patients, the SD of the percent change from baseline in TGs is considered approximately 46%. Based on the sample size consideration (14:14:14) it was planned to have a 90% power to detect a 60% difference between each olezarsen (ISIS 678354) treatment group and pooled placebo group at an alpha level of 0.05 (two-sided), assuming 60% reduction in the ISIS 678354 treatment patients and no change in the placebo patients. Primary analysis showed that the estimated effect per comparison with 80 mg olezarsen and placebo is 43.5%. The difference of achieved decrease in fasting TG level is considered modest and, despite the statistical significance, did not reach the pre-specified threshold of 60% difference between treatment group and pooled placebo group. The estimated effect per comparison with 50 mg olezarsen and placebo did not reach statistical significance and difference between treatment group and pooled placebo group was only ~ -22%. Considering the type 1 error control strategy applied, statistical testing for the secondary endpoints on the comparison between olezarsen 80 mg and 50 mg versus placebo were of exploratory nature. Comparison between olezarsen versus placebo were performed at the two-sided 0.05 significance level and no multiplicity adjustments was performed. The study-wise Type I error rate was therefore not adequately controlled for the secondary endpoints, and the chance of erroneously finding a treatment effect on at least one of the secondary endpoints is much more than 5%. A particular concern arises over the robustness of data on pancreatitis rate that further comes from the limited sample size leading to a wide interval confidence and poor precision of the estimate as well as the limited time for observations. Moreover, the responder rate was low in both olezarsen groups compared placebo group, as targeted ≥ 70% decrease in fasting TG at Month 6 in the 80 mg olezarsen group was only 9.1% (n=2) and none of the patients achieved a ≥ 70% decrease in fasting TG in the placebo group. There was no nominal statistically significance difference between groups (nominal p=0.2802). Data from large healthcare databases suggest that sustained hypertriglyceridemia (>500 mg/dL) increases the risk of pancreatitis (hazard ratio 1.79 [CI 95%: 1.10-1.28]) (Christian JB et al, 2012). Lowering TG from >500 mg/dL to less than 200 mg/dL can reduce the incidence of acute pancreatitis from 1.1 to 0.4 per 100 person-year (adjusted OR 0.45 [CI 95%: 0.34-0.60]) (Christian JB et al, 2014; Okazaki H et al, 2021). A TG level > 880 mg/dL has been shown to be associated with persistent chylomicronemia and the risk of acute pancreatitis is still greater compared with lower TG levels for which chylomicrons are not consistently observed (Sanchez et al. 2021). The results of the primary analysis from the pivotal study ISIS 678354-CS3 demonstrated that the average level of fasting TG level at Month 6 was 1731.9 (± 1204.26) mg/dL in the olezarsen 80 mg group, which is as much as twice higher as the targeted 880 mg/dL. Therefore, after 6 months of treatment with 80 mg olezarsen, the persistent chylomicronemia is considered to be sustained despite the 31,99% reduction in the fasting TG level at Month 6 from baseline and, despite the treatment with olezarsen, diet and concomitant use of lipid lowing medicines, patients are still at high risk of acute pancreatitis. The average level of fasting TG level in the olezarsen 50 mg group did not decrease below 2000 mg/dL and was 2086.8 (±807.48), i.e. -10,85% from baseline to Month 6.

In general, the secondary (exploratory) endpoints' results reflected the mechanism of action of olezarsen. Specifically, the decrease in fasting TG and apoB-III levels were pronounced compared with placebo. The percent change in fasting apoC-III from baseline to Month 6 and Month 12 decreased significantly in the 80 mg olezarsen group compared with placebo group: -66.13% and -64.20%, respectively, vs 17.08% (nominal p<0.0001).

In the 80 mg olezarsen group percent of change in fasting apoB-48 from baseline to Month 6 was significantly bigger (-59.49%) compared with placebo group (24.50%) (nominal p=0.0019). The percent of change in fasting apoB-48 at Month 12 further decreased compared with baseline value (-

79.15%), but this difference did not reach the nominal statistical significance compared with placebo at Month 12 (-3.52%) (nominal p=0.0560). There was no meaningful difference in change of apoB-48 from baseline to Month 6 and Month 12 in the 50 mg olezarsen group and placebo group, although the fasting level of apoB-48 had a slight further decrease from Month 6 to Month 12 in the olezarsen group. It is known that fatty meals induce intestinal secretion of chylomicrons (CMs) containing apolipoprotein (Apo) B48. ApoB48 is produced after post-transcriptional RNA modification by Apobec-1 editing enzyme, exclusively in the small intestine of humans (Lo CC and Coschigano KT., 2020). ApoB48 serves as the main structural apolipoprotein of TG-rich lipoproteins for transporting dietary lipids from the small intestine to peripheral tissues, particularly adipose tissue and the skeletal muscle (Tso and Balint, 1986; Kohan et al., 2015). These dietary lipids are shunted into peripheral tissues to provide energy and to protect the liver from excessive accumulation of TG and/or precursors of TG (Xiao et al., 2011). Since one role of CM is to transfer exogenous lipids derived from food to the liver or peripheral tissues, the measurement of Apo B-48 is considered a best marker for observation of exogenous lipid transportation after food intake. There was no difference in ApoB-48 at Month 12 in both group of olezarsen compared with placebo group and, therefore, it could be hypothesized that apoB-48 levels were much more affected by the patients' adjunction to the diet during the study rather than treatment with olezarsen.

Other secondary endpoints were nominally statistically significant better in favour of olezarsen 80 and 50 mg. At Month 6, also non-HDL-C levels were reduced by 24.20% (95% CI: -40.484, -7.911) and 17.69% (95% CI: -34.571, -0.801) for the olezarsen 80 mg and olezarsen 50 mg groups, respectively (nominal p-value = 0.0036 and 0.0401 for the olezarsen 80 mg group and olezarsen 50 mg group, respectively, versus placebo), with similar effects observed at month 12 (39.70% (95% CI: -63.108, -16.292) and 29.84% (95% CI: -53.490, -6.198) for the olezarsen 80 mg and olezarsen 50 mg groups, respectively; nominal p-value = 0.0009 and 0.0134, respectively).

Overall, the results of the lipid profile in the treated patients at Month 6 and 12 might be considered clinically relevant compared with placebo, but quite modest in regard with a decrease in the fasting TG and apoB-III levels demonstrated in the pivotal study with volanesorsen. The proportion of patients who achieved TG level ≤ 880 mg/dL from baseline to Month 6 and Month 12 was small in the 80 mg olezarsen group. However, the rate of adjudicated acute pancreatitis was shown to be lower in the pooled olezarsen groups compared to placebo (4.7% vs 36.31% respectively), and it was therefore considered that the demonstrated trend towards a reduction in the incidence of pancreatitis at week 53 provided support to the claim of clinical relevance of the treatment effect. Although it is shown within a limited treatment timeframe, it could be agreed that based on the results of the Balance study the observed decrease in fasting TG levels led to the reduction in the rate of acute pancreatitis in FCS patients treated with olezarsen. Nevertheless, the CHMP considers that the addition of a withdrawal rule should be added to the SmPC. The withdrawal proposal is related to the efficacy data from the Balance study, in which 22 % of patient did not have reduction of fasting TG level either on Month 6 or Month 12. A waterfall plot of percentage change (%) in fasting TG levels at Month 3 and Month 6 in the Balance study was provided by the Applicant and, based on this, the CHMP recommended to add the following sentence in Section 4.2 of SmPC: "Some patients might not be responsive to the treatment after 6 months, in such a case the discontinuation of olezarsen should be considered on an individual basis by the prescribing physician." Although from the efficacy point of view some reservations exist regarding the chosen dose of 80 mg/4 weeks for the clinical trials, this dose demonstrated substantially better safety compared with that available in clinical practice, i.e. volanesorsen. There was a lower share of patients who experienced thrombocytopenia compared with already available in clinical practice volanesorsen. None of patients in the olezarsen 80 mg group and the placebo group experienced thrombocytopenia in the Balance study. No patient in any treatment group met predefined stopping rule regarding platelet counts leading to Study Drug discontinuation, or discontinued treatment due to a thrombocytopenia TEAE. None of patients with platelet count < lower limit of

normal (LLN) experienced a concurrent serious or severe clinical bleeding event. Moreover, olezarsen could be used in previously excluded sub-groups patients – patients with platelet count platelet count from < 140 × 10^9/L to < 100 × 10^9/L (volanesorsen is contraindicated to be used in this patient population due to significant safety concerns).

Overall, supplementary analyses showed similar results as the primary analysis. Thus, no concern could be raised. Given the very limited sample size of study CS3, the pre-specified subgroup analysis offers very limited value in the assessment of data.

However, there was an uncertainty/concern regarding the large fluctuations in fasting TG levels observed in the open-label extension study (ISIS 678354-CS13), which needed to be resolved. Therefore, the latest long-term observation data was necessary to conclude on the clinical efficacy of olezarsen 80 mg and further characterise whether in the longer term a reduction in pancreatitis events, or other clinically relevant events including abdominal pain and quality of life (QoL), is maintained. The applicant was requested to provide a comprehensive resume of the primary and secondary results from the OLE study (ISIS 678354-CS13) and ISIS 678354-CS7 study by Month 3, 6, 12, 18 and 24 to see the evolution of mean fasting TG and apoC-III average levels from baseline in the olezarsen 80 mg group compared with placebo.

In their response, the applicant has provided the comprehensive resume of the primary and secondary results from the OLE study (ISIS 678354-CS13) and ISIS 678354-CS7 study by Month 3, Month 6, Month 12, Month 18 and Month 24 as requested. Overall, sustained decrease in fasting TG and apoC-III levels (assessed as a median % change) has been observed up to Week 129 (CS0133). The percent change in apoC-III levels have been maintained within from approximately - 60% to - 80% from baseline level, while a median % change in fasting TG level ranged from approximately 40% at week 5 to approximately -30% at week 129. During the follow-up period there were some fluctuations of up and down in the relative decrease of fasting TG and apoC-III levels which could be considered acceptable, except –9.53% at week 105 in OLE study (CS13) Baseline to OLE (CS13) Treatment period.

In patients treated previously with volanesorsen (study ISIS 678354-CS7) the percent change (assessed as a median % change) in fasting TG and apoC-III levels were from approximately - 30% to 65% in apoC-III levels and from approximately -20% at week 5 to –30% at week 157. Unexplained high level of fasting TG was identified at week 37 of follow-up. In general, the reduction in fasting TG and apoC-III levels in patients previously treated with volanesorsen could be characterized as modest compared with those in naive treated patients.

To conclude the currently available data for patients treated up to 2.5 years in ISIS 678354-CS13 and up to 3 years in ISIS 678354-CS7 show sustained decrease in fasting TG and apoC-III levels from baseline. Some fluctuations in fasting TG and apoC-III should be expected during the treatment of patients, but a long-term decrease in fasting TG and apoC-III levels has been observed on treatment with olezarsen.

Based on the pivotal study results, a statistically significant reduction in the incidence of pancreatitis was reported in patients treated with 50 mg and 80 mg of olezarsen. These results generally demonstrate that a consistent reduction in the increased levels of chylomicronemia lowers the risk of pancreatitis compared with placebo.

The differences in annualized all cause hospitalization rates, the annualized rate of inpatient days and the annualized number of ER visits for the total olezarsen group and both olezarsen treatment groups compared with the placebo group were nominally significant. The Patient Global Impression Assessment showed a difference in favour of olezarsen compared to placebo at Month 6. However, it was nominally significant for the olezarsen 80 mg group (nominal p-value = 0.0393), but not the 50

mg olezarsen group (nominal p-value= 0.5288). At Month 12 the Patient Global Impression Assessment results were not consistent as it did not show nominally statistically significant difference in favour of 80 mg olezarsen compared to placebo (nominal p-value = 0.1026). The exploratory analysis of change from Baseline (without or with a 2-week recall) for the FCS Symptoms and Impacts Scales (FCS-SIS) symptoms and impacts item and composite scores did not identify change from Baseline differences, compared with placebo, for the olezarsen 80 mg group and the olezarsen 50 mg group. However, it could be agreed that due to the small sample size and highly subjective nature of the evaluation question significant changes are difficult to detect and interpret. The conduct of study ISIS 678354 CS3 is considered adequate and a routine GCP inspection has not been requested. No clear trigger for a GCP inspection has been identified after a review of clinical data.

The results from the study *678354-CS8* were provided by the applicant to support the efficacy results from the pivotal study. The study ISIS 678354-CS8 data are considered supportive as they clearly show that olezarsen targets apoC-III mRNA. Consequently, the inhibition of the translation of apoC-III mRNA by olezarsen (both 50 and 80 mg) leads to the reduction of apoC-III and serum TG levels in patients with hypertriglyceridemia and atherosclerotic cardiovascular disease (established or at increased risk for), and/or with severe hypertriglyceridemia. However, the main limitation of this study that the patients with FCS were not included in the study population. Therefore, these data have low informative value in the light of efficacy of treatment of patients with FCS but clearly demonstrate the pharmacological effect of olezarsen on TG level.

The applicant did not include the data from the study ISIS 678354-CS8 in the SmPC of olezarsen. The CHMP view is that provided data from *678354-CS8 study* are not relevant for the sought indication. Of note, a non-significant increase in LDL-C and a more pronounced rise in HDL-C were observed in the treatment groups relative to placebo (+ 48.01% (95% CI: 37.18, 58.83) and + 48.02% (95% CI: 37.00, 59.04) in the 80 mg and 50 mg olezarsen groups compared to + 8.38 (95% CI: (-3.70, 20.46) of placebo; p<0.0001 for both doses versus placebo).The HDL-C and LDL-C were not profiled in the pivotal CS3 trial, and the treatment effect on these parameters in the target population remains undetermined. Considering the mode of action of the drug, an antiatherogenic effect for olezarsen can be assumed deriving from the apoC-III suppression, on the basis of genetic studies showing that carriers of loss-of-function mutations in apoC-IIIhad ~40% lower risk of atherosclerotic cardiovascular disease, ASCVD (clinical and subclinical) compared to noncarriers (Pollini et al. 2008). Nevertheless, the long-term cardiovascular safety of treatment needs to be monitored through pharmacovigilance activity in order to intercept any potential signal arising from the clinical use of the drug in the target population.

Considering data of the extension observation OLE study (ISIS 678354-CS13), the ancillary analysis of the efficacy data was provided by the applicant (*interim analysis*). Fasting TG levels during Month 12 of observation were not consistently maintained at the level achieved at Month 12 of the pivotal study in the 80 mg olezarsen group of patients. In general, during the first 12 month of OLE study there were considerable fluctuations in fasting TG level in the 80 mg olezarsen group, which needed to be explained by the applicant. The applicant has provided the comprehensive resume of the primary and secondary results from the OLE study (ISIS 678354-CS13) and ISIS 678354-CS7 study by Month 3, Month 6, Month 12, Month 18 and Month 24 as requested. Overall, sustained decrease in fasting TG and apoC-III levels (assessed as a median % change) has been observed up to Week 129 (CS0133). The percent change in apoC-III levels have been maintained within from approximately - 60% to -80% from baseline level, while a median % change in fasting TG level ranged from approximately 40% at week 5 to approximately -30% at week 129. During the follow-up period there were some fluctuations of up and down in the relative decrease of fasting TG and apoC-III levels which could be considered acceptable, except –9.53% at week 105 in OLE study (CS13) Baseline to OLE (CS13) Treatment period. Patients who switched from placebo to 80 mg of olezarsen/every 4 weeks, achieved

about 30% reduction in mean of fasting TG level from baseline of OLE study at Month 6 of the OLE study and it was maintained at the same level at Month 12. Fasting TG level of patients from the 50 mg olezarsen group continued increasing from OLE baseline through Month 6 up to Month 12. The mean event rate of acute pancreatitis event in the pooled olezarsen group (80 mg +50 mg) was significantly lower compared with placebo group: 4.37/100 pts year (95% CI 0.942- 20.298) and 36.3/ 100 pts year (95% CI 14.700- 89.685) ($_{nominal}$p =0.0144), supporting the benefit of the treatment

2.5.7. Conclusions on the clinical efficacy

The efficacy data obtained in the pivotal study ISIS 678354-CS3 showed a statistically significant decrease in fasting TG level from baseline to Month 6 in patients treated with 80 mg of olezarsen, but not with 50 mg of olezarsen. Despite the statistically significant difference compared with placebo, the recommended maintenance of plasma TG levels below 500-1000 mg/dL was not achieved in both olezarsen groups at Month 6 and Month 12, as well as predefined 60% difference between each olezarsen treatment group and pooled placebo group at the time of primary analysis (Month 6). Therefore, the magnitude of effect in terms of relative decrease in fasting TG level is considered quite modest in patients treated with 80 mg of olezarsen/every 4 weeks compared to placebo (43,5%). As the primary endpoint in the 50 mg olezarsen group did not reach the statistical significance, the pre-specified secondary endpoints are considered only exploratory based on the pre-specified hierarchical testing procedure. Overall, the decrease in the lipid levels were observed in both olezarsen groups compared with placebo. The responder rate was defined as the proportion of patients achieving a targeted ≥ 70% decrease in fasting TG at Month 6. More patients achieved ≥ 40% decrease in fasting at Month 6 in the 80 mg olezarsen group than in the placebo group. However, there was no statistically significant difference between the 80 mg olezarsen group and placebo group in the proportion of patients who achieved ≥ 70% decrease in fasting TG at Month 6. The proportion of patients who achieved TG level ≤ 880 mg/dL from baseline to Month 6 and Month 12 was small in the 80 mg olezarsen group, considering the previous study results in patients with FCS.

Overall, the results of the lipid profile in the treated patients at Month 6 and 12 might be considered clinically relevant compared with placebo. Pancreatitis is the most serious comorbidity resulting from high persistent triglycerides levels. Based on the pivotal study results, a statistically significant reduction in the incidence of pancreatitis was reported in patients treated with 50 mg and 80 mg of olezarsen. These results generally demonstrate that reducing levels of plasma chylomicronemia lowers the risk of pancreatitis. No patient in any olezarsen treatment group met predefined stopping rule regarding platelet counts leading to Study Drug discontinuation, or discontinued treatment due to a thrombocytopenia TEAE. None of patients with platelet count < lower limit of normal (LLN) experienced a concurrent serious or severe clinical bleeding event. Additionally, olezarsen could be used in previously excluded sub-groups patients – patients with platelet count from < 140 × 10^9/L to < 100 × 10^9/L (volanesorsen is contraindicated to be used in this patient population due to significant safety concerns). Although it is shown within a limited treatment timeframe, it could be agreed that based on the results of the Balance study the observed decrease in fasting TG levels led to the reduction in the rate of acute pancreatitis in FCS patients treated with olezarsen. Thus, with the limit of an exploratory analysis and low precision of the estimate, data can be taken as supportive of clinical relevance for olezarsen, provided that the indication clearly reflects the study population of the pivotal trial.

The long-term efficacy studies are ongoing, meanwhile the currently available data for patients treated up to 2.5 years in ISIS 678354-CS13 and up to 3 years in ISIS 678354-CS7 show sustained decrease in fasting TG and apoC-III levels from baseline. Some fluctuations in fasting TG and apoC-III should be expected during the treatment of patients, but a long-term decrease in fasting TG and apoC-III levels has been observed on treatment with olezarsen. However, based on the results of the Balance study,

the decrease in fasting TG levels resulted in a reduction in the rate of acute pancreatitis (AP) within a limited treatment timeframe.

2.5.8. Clinical safety

Clinical programme of olezarsen evaluating safety consists of 5 clinical studies.

Main safety data:

Phase 3 studies in patients with FCS

ISIS 678354-CS3/Balance - a randomized, double-blind, placebo-controlled study. CS3 was the study from which the primary conclusions for the safety of olezarsen in patients with FCS were derived.
ISIS 678354-CS13 - an open-label extension of above CS3 study.
ISIS 678354-CS7/Switch - an open-label safety study in patients with FCS previously treated with volanesorsen.

Additional safety data:

Phase 2 studies in patients with other than FCS indication

ISIS 678354-CS2 - multicenter, randomized, double-blind, placebo-controlled, dose-ranging study in patients with hypertriglyceridemia and established CVD or at high risk for CVD.
ISIS 678354-CS8 - multi-center, randomized, double-blind, placebo-controlled study performed in patients with hypertriglyceridemia and established or increased risk of atherosclerotic CVD, and/or with severe hypertriglyceridemia.

Study CS3 is the one from which the primary conclusions for the safety of olezarsen in patients with FCS are derived from. Safety data from study CS8 provide supportive information from patients with HTG and established or increased risk of ASCVD, or with sHTG for the overall safety profile of olezarsen.

Safety data was pooled in order to confirm safety findings identified in the individual patient studies based upon a larger, integrated dataset or to determine if any other safety observations would be revealed that were not otherwise evident in the individual clinical studies. The list of integrated pools is provided below:

Pool 1: Pivotal and confirmatory efficacy: randomized, double-blind, placebo-controlled studies (CS3 + CS8). This pool provides a safety evaluation of patients from the randomized, double-blind, placebo-controlled pivotal Study CS3 and confirmatory efficacy Study CS8. Due to the differences in study designs and study populations between these 2 studies, the data from CS3 and CS8 are presented side by side in parallel to Pool 1 to allow a comparative review of the overall safety profile.
Pool 2: Randomized, double-blind, placebo-controlled study in FCS + hypertriglyceridemia and atherosclerotic cardiovascular disease, or severe hypertriglyceridemia population (CS3 + CS8 + CS2).
Pool 3: Long-term open-label studies in FCS population (CS7 + CS13).
Pool 4: All FCS population studies (CS3 + CS13 + CS7). This pool supports data from Pool 1 and provides a safety evaluation for all patients in the FCS population.

Pool 5: All patient population studies (CS3 + CS13 + CS7 + CS2 + CS8).

In this Overview, the main focus is on data from Pool 1 and Pool 4.

2.5.8.1. Patient exposure

In total, 378 patients participated in clinical development programme (5 studies) of olezarsen. Of them, 292 patients received at least 1 dose of olezarsen. Across all 5 studies, 245 patients were exposed to study treatment for 12 months or more.

Pool 1 (CS3 + CS8): Patient Demographics and Baseline Characteristics

Patients from study CS3 had a lower overall Baseline mean (±SD) age (45.0 [13.38] years) compared with patients from CS8 (61.8 [10.24] years).

Patients from study CS3 had a lower overall Baseline mean (±SD) body weight (65.914 [15.1374] kg) and BMI (23.94 [4.711] kg/m2) compared with patients from study CS8 (97.259 [23.6755] kg and 33.86 [6.460] kg/m2, respectively). In addition, there was a greater proportion of patients with a medical history of diabetes mellitus in CS8 (68.2% overall) compared with CS3 (24.2% overall).

Similarly, FCS patients from study CS3 had greater overall Baseline mean (±SD) fasting TG (2629.5 [1315.45] mg/dL), fasting apoC-III (27.652 [11.1152] mg/dL), and fasting TC (295.00 [105.266] mg/dL) compared with patients from study CS8 (303.2 [201.70] mg/dL, 16.410 [6.6927] mg/dL, and 178.9 [46.28] mg/dL, respectively).

However, since these differences between study population characteristics were balanced across the 3 treatment groups, demographic and Baseline characteristics of Pool 1 were generally similar across the 3 treatment groups. In Pool 1, the mean patient age at Baseline was 56.8 years in the olezarsen 80 mg group, 57.2 years in the olezarsen 50 mg group, and 56.1 years in the placebo group; overall, 150 patients were < 65 years (54 [68.4%], 53 [67.1%], and 43 [69.4%] in the olezarsen 80 mg group, olezarsen 50 mg group, and placebo group, respectively), and 70 patients were ≥ 65 years (25 [31.6%], 26 [32.9%], and 19 [30.6%] in the olezarsen 80 mg group, olezarsen 50 mg group, and placebo group, respectively). The proportion of female patients was slightly lower in the olezarsen 80 mg group compared with the olezarsen 50 mg group and the placebo group (28 [35.4%] patients compared with 39 [49.4%] and 36 [58.1%], respectively).

Across all treatment groups, the majority of patients were White (87.3% in the olezarsen 80 mg group, 89.9% in the olezarsen 50 mg group, and 90.3% in the placebo group).

Mean (±SD) BMI at Baseline was similar across the treatment groups: 30.58 (6.876) kg/m^2 in the olezarsen 80 mg group, 31.30 (8.176) kg/m^2 in the olezarsen 50 mg group, and 30.74 (7.518) kg/m^2 in the placebo group.

Pool 4 (CS3 + CS13 + CS7, all FCS patients): Patient Demographics and Baseline Characteristics

Table 34: Summary of Demographics– All FCS Patients (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
System Organ Class Preferred Term	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Age (years)				
n	23	21	66	87

Mean (SD, SEM)	44.0 (14.67, 3.06)	43.2 (12.11, 2.64)	46.7 (13.33, 1.64)	45.9 (13.07, 1.40)
Median (P25, P75)	46.0 (32.0, 55.0)	42.0(38.0, 48.0)	47.0(37.0, 57.0)	46.0 (37.0, 56.0)
Minimum, maximum	21, 69	18, 74	23, 78	18, 78
Mean 95% CI	37.7, 50.3	37.7, 48.7	43.4, 50.0	43.1, 48.7
Age Group - n (%)				
< 65	20 (87.0)	20 (95.2)	60 (90.9)	80 (92.0)
≥ 65	3 (13.0)	1 (4.8)	6 (9.1)	7 (8.0)
Gender – n (%)				
Male	11 (47.8)	6 (28.6)	31 (47.0)	37 (42.5)
Female	12 (52.2)	15 (71.4)	35 (53.0)	50 (57.5)
Race – n (%)				
Asian	0	3 (14.3)	5 (7.6)	8 (9.2)
Black or African American	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (4.8)	0	1 (1.1)
White	22 (95.7)	17 (81.0)	57 (86.4)	74 (85.1)
Multiple	0	0	0	0
Other	1 (4.3)	0	4 (6.1)	4 (4.6)
Ethnicity – n (%)				
Hispanic or Latino	3 (13.0)	3 (14.3)	3 (4.5)	6 (6.9)
Not Hispanic or Latino	20 (87.0)	18 (85.7)	63 (95.5)	81 (93.1)

Across all treatment groups except for the olezarsen 10-40 mg group, demographics and Baseline characteristics were largely similar to Pool 1 and Pool 4.

2.5.8.2. Adverse events

Across all studies and pools, the proportion of patients who experienced TEAEs was similar or greater in the placebo group compared with the olezarsen groups, the majority of TEAEs experienced by patients in all treatment groups were mild or moderate in severity, the proportion of patients who experienced TEAEs related to study drug was greater in the olezarsen treatment groups compared with the placebo group, and the proportion of patients who experienced serious TEAEs was similar or greater in the placebo group compared with the olezarsen treatment groups.

Pool 1

Table 35: Treatment-Emergent Adverse Events in > 5% of Patients in Any Treatment Group in CS3, CS8, or Pool 1 by System Organ Class and Preferred Term

	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
System Organ Class Preferred Term	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with At Least One TEAE, n (%)	22 (95.7)	18 (85.7)	19 (86.4)	37 (86.0)	30 (76.9)	43 (74.1)	38 (66.7)	81 (70.4)	52 (82.7)	61 (77.7)	57 (72.7)	118 (75.2)
Blood and lymphatic system disorders												
Anaemia	1 (4.3)	0	2 (9.1)	2 (4.7)	0	1 (1.7)	2 (3.5)	3 (2.6)	1 (1.3)	1 (1.2)	4 (5.2)	5 (3.2)
Gastrointestinal disorders												
Abdominal distension	0	0	2 (9.1)	2 (4.7)	0	0	0	0	0	0	2 (2.8)	2 (1.4)
Abdominal pain	8 (34.8)	3 (14.3)	4 (18.2)	7 (16.3)	0	1 (1.7)	2 (3.5)	3 (2.6)	8 (10.7)	4 (5.6)	6 (8.0)	10 (6.8)
Abdominal pain upper	1 (4.3)	2 (9.5)	2 (9.1)	4 (9.3)	0	0	1 (1.8)	1 (0.9)	1 (1.3)	2 (2.9)	3 (4.0)	5 (3.5)
Dental caries	2 (8.7)	0	0	0	0	0	0	0	2 (2.7)	0	0	0
Diarrhoea	6 (26.1)	1 (4.8)	2 (9.1)	3 (7.0)	0	2 (3.4)	1 (1.8)	3 (2.6)	6 (8.0)	3 (3.9)	3 (4.0)	6 (3.9)
Gastrooesophageal reflux disease	2 (8.7)	0	0	0	0	1 (1.7)	0	1 (0.9)	2 (2.7)	1 (1.2)	0	1 (0.6)
Nausea	1 (4.3)	2 (9.5)	1 (4.5)	3 (7.0)	1 (2.6)	1 (1.7)	1 (1.8)	2 (1.7)	2 (3.1)	3 (4.1)	2 (2.6)	5 (3.3)
Pancreatitis	4 (17.4)	2 (9.5)	1 (4.5)	3 (7.0)	0	0	0	0	4 (5.3)	2 (2.9)	1 (1.4)	3 (2.1)
Pancreatitis acute	3 (13.0)	0	0	0	0	1 (1.7)	0	1 (0.9)	3 (4.0)	1 (1.2)	0	1 (0.6)

Pancreatitis necrotising	2 (8.7)	0	0	0	0	0	0	0	2 (2.7)	0	0	0
Vomiting	0	1 (4.8)	2 (9.1)	3 (7.0)	0	0	0	0	0	1 (1.5)	2 (2.8)	3 (2.1)
General disorders and administration site conditions												
Fatigue	4 (17.4)	1 (4.8)	1 (4.5)	2 (4.7)	1 (2.6)	6 (10.3)	1 (1.8)	7 (6.1)	5 (7.1)	7 (8.6)	2 (2.6)	9 (5.6)
Injection site erythema	1 (4.3)	1 (4.8)	2 (9.1)	3 (7.0)	0	8 (13.8)	2 (3.5)	10 (8.7)	1 (1.3)	9 (11.0)	4 (5.2)	13 (8.2)
Injection site pain	0	2 (9.5)	1 (4.5)	3 (7.0)	0	1 (1.7)	0	1 (0.9)	0	3 (4.1)	1 (1.4)	4 (2.7)
Infections and infestations												
Acute sinusitis	0	0	0	0	1 (2.6)	1 (1.7)	3 (5.3)	4 (3.5)	1 (1.8)	1 (1.2)	3 (3.6)	4 (2.4)
Bronchitis	0	0	0	0	3 (7.7)	3 (5.2)	0	3 (2.6)	3 (5.3)	3 (3.6)	0	3 (1.8)
COVID-19	8 (34.8)	6 (28.6)	3 (13.6)	9 (20.9)	2 (5.1)	5 (8.6)	4 (7.0)	9 (7.8)	10 (14.2)	11 (14.7)	7 (9.0)	18 (11.8)
Cellulitis	3 (13.0)	0	0	0	2 (5.1)	1 (1.7)	2 (3.5)	3 (2.6)	5 (7.6)	1 (1.2)	2 (2.4)	3 (1.8)
Influenza	2 (8.7)	3 (14.3)	1 (4.5)	4 (9.3)	0	2 (3.4)	1 (1.8)	3 (2.6)	2 (2.7)	5 (6.8)	2 (2.6)	7 (4.7)
Nasopharyngitis	1 (4.3)	2 (9.5)	1 (4.5)	3 (7.0)	2 (5.1)	2 (3.4)	3 (5.3)	5 (4.3)	3 (4.9)	4 (5.3)	4 (5.0)	8 (5.2)
Pyelonephritis	0	0	0	0	2 (5.1)	0	0	0	2 (3.6)	0	0	0
Upper respiratory tract infection	0	2 (9.5)	0	2 (4.7)	2 (5.1)	1 (1.7)	2 (3.5)	3 (2.6)	2 (3.6)	3 (4.1)	2 (2.4)	5 (3.2)
Urinary tract infection	0	3 (14.3)	1 (4.5)	4 (9.3)	6 (15.4)	6 (10.3)	3 (5.3)	9 (7.8)	6 (10.7)	9 (11.6)	4 (5.0)	13 (8.3)
Sinusitis	0	0	0	0	4 (10.3)	1 (1.7)	1 (1.8)	2 (1.7)	4 (7.1)	1 (1.2)	1 (1.2)	2 (1.2)
Injury, poisoning and procedural complications												

Arthropod bite	0	2 (9.5)	0	2 (4.7)	0	0	0	0	0	2 (2.9)	0	2 (1.4)
Fall	0	0	0	0	2 (5.1)	0	1 (1.8)	1 (0.9)	2 (3.6)	0	1 (1.2)	1 (0.6)
Skin abrasion	0	0	0	0	2 (5.1)	0	0	0	2 (3.6)	0	0	0
Skin laceration	2 (8.7)	1 (4.8)	1 (4.5)	2 (4.7)	0	0	0	0	2 (2.7)	1 (1.5)	1 (1.4)	2 (1.4)
Investigations												
Alanine aminotransferase increased	1 (4.3)	0	1 (4.5)	1 (2.3)	0	3 (5.2)	3 (5.3)	6 (5.2)	1 (1.3)	3 (3.6)	4 (5.0)	7 (4.3)
Blood creatine phosphokinase increased	0	0	0	0	1 (2.6)	0	3 (5.3)	3 (2.6)	1 (1.8)	0	3 (3.6)	3 (1.8)
Glomerular filtration rate decreased	0	0	0	0	3 (7.7)	1 (1.7)	0	1 (0.9)	3 (5.3)	1 (1.2)	0	1 (0.6)
Liver function test increased	0	0	0	0	0	3 (5.2)	1 (1.8)	4 (3.5)	0	3 (3.6)	1 (1.2)	4 (2.4)
Platelet count decreased	1 (4.3)	1 (4.8)	3 (13.6)	4 (9.3)	0	0	1 (1.8)	1 (0.9)	1 (1.3)	1 (1.5)	4 (5.4)	5 (3.5)
Metabolism and nutrition disorders												
Diabetes mellitus	0	0	0	0	1 (2.6)	4 (6.9)	4 (7.0)	8 (7.0)	1 (1.8)	4 (4.8)	4 (4.9)	8 (4.8)
Hypoglycaemia	2 (8.7)	1 (4.8)	1 (4.5)	2 (4.7)	0	0	0	0	2 (2.7)	1 (1.5)	1 (1.4)	2 (1.4)
Hyponatraemia	2 (8.7)	0	0	0	0	0	0	0	2 (2.7)	0	0	0
Type 2 diabetes mellitus	1 (4.3)	0	0	0	2 (5.1)	1 (1.7)	1 (1.8)	2 (1.7)	3 (4.9)	1 (1.2)	1 (1.2)	2 (1.2)
Musculoskeletal and connective tissue disorders												
Arthralgia	0	3 (14.3)	1 (4.5)	4 (9.3)	2 (5.1)	5 (8.6)	0	5 (4.3)	2 (3.6)	8 (10.4)	1 (1.4)	9 (5.9)
Back pain	2 (8.7)	0	1 (4.5)	1 (2.3)	1 (2.6)	5 (8.6)	1 (1.8)	6 (5.2)	3 (4.4)	5 (6.0)	2 (2.6)	7 (4.3)
Pain in extremity	1 (4.3)	2 (9.5)	3 (13.6)	5 (11.6)	0	1 (1.7)	2 (3.5)	3 (2.6)	1 (1.3)	3 (4.1)	5 (6.6)	8 (5.4)

Nervous system disorders												
Headache	3 (13.0)	4 (19.0)	1 (4.5)	5 (11.6)	1 (2.6)	1 (1.7)	2 (3.5)	3 (2.6)	4 (5.8)	5 (7.0)	3 (3.8)	8 (5.4)
Migraine	2 (8.7)	1 (4.8)	0	1 (2.3)	0	0	0	0	2 (2.7)	1 (1.5)	0	1 (0.7)
Syncope	1 (4.3)	0	0	0	2 (5.1)	0	1 (1.8)	1 (0.9)	3 (4.9)	0	1 (1.2)	1 (0.6)
Psychiatric disorders												
Anxiety	0	3 (14.3)	0	3 (7.0)	1 (2.6)	1 (1.7)	0	1 (0.9)	1 (1.8)	4 (5.6)	0	4 (2.7)
Renal and urinary disorders												
Dysuria	0	1 (4.8)	0	1 (2.3)	2 (5.1)	0	0	0	2 (3.6)	1 (1.5)	0	1 (0.7)
Proteinuria	2 (8.7)	0	0	0	1 (2.6)	1 (1.7)	0	1 (0.9)	3 (4.4)	1 (1.2)	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders												
Cough	2 (8.7)	2 (9.5)	2 (9.1)	4 (9.3)	2 (5.1)	1 (1.7)	3 (5.3)	4 (3.5)	4 (6.2)	3 (4.1)	5 (6.4)	8 (5.3)
Epistaxis	1 (4.3)	2 (9.5)	0	2 (4.7)	0	0	1 (1.8)	1 (0.9)	1 (1.3)	2 (2.9)	1 (1.2)	3 (2.0)
Upper respiratory tract congestion	0	0	0	0	2 (5.1)	1 (1.7)	0	1 (0.9)	2 (3.6)	1 (1.2)	0	1 (0.6)
Vascular disorders												
Hypertension	1 (4.3)	1 (4.8)	0	1 (2.3)	2 (5.1)	2 (3.4)	1 (1.8)	3 (2.6)	3 (4.9)	3 (3.9)	1 (1.2)	4 (2.5)

Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100.Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.
Note: Adverse events were coded using MedDRA Version 26.0.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.
Note: Percentages are rounded to one decimal place; however, actual values were used to determine the > 5.0% cutoff (e.g., value may be rounded down to 5.0%, but actual value is 5.02, which is > 5.0%).
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse even

In Pool 1, 13.8% of patients in placebo group had at least one severe AE, comparing with 5% and 6.5% in olezarsen 80 mg group and total olezarsen group, respectively.

Pool 4 (CS3 + CS7 + CS13)

Table 36: Treatment-Emergent Adverse Events in > 5% of Patients in Any Treatment Group by System Organ Class and Preferred Term (Pool 4)

System Organ Class Preferred Term	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Patients with At Least One TEAE, n (%)	22 (95.7)	19 (90.5)	58 (87.9)	77 (88.5)
Infections and infestations				
COVID-19	8 (34.8)	10 (47.6)	13 (19.7)	23 (26.4)
Influenza	2 (8.7)	6 (28.6)	6 (9.1)	12 (13.8)
Nasopharyngitis	1 (4.3)	4 (19.0)	4 (6.1)	8 (9.2)
Upper respiratory tract infection	0	2 (9.5)	3 (4.5)	5 (5.7)
Urinary tract infection	0	3 (14.3)	2 (3.0)	5 (5.7)
Cellulitis	3 (13.0)	0	0	0
Gastrointestinal disorders				
Abdominal pain	8 (34.8)	3 (14.3)	15 (22.7)	18 (20.7)
Nausea	1 (4.3)	2 (9.5)	7 (10.6)	9 (10.3)
Vomiting	0	1 (4.8)	7 (10.6)	8 (9.2)
Pancreatitis	4 (17.4)	2 (9.5)	5 (7.6)	7 (8.0)
Abdominal pain upper	1 (4.3)	2 (9.5)	4 (6.1)	6 (6.9)
Diarrhoea	6 (26.1)	1 (4.8)	5 (7.6)	6 (6.9)
Gastrooesophageal reflux disease	2 (8.7)	1 (4.8)	0	1 (1.1)
Pancreatitis acute	3 (13.0)	0	1 (1.5)	1 (1.1)
Dental caries	2 (8.7)	0	0	0
Pancreatitis necrotising	2 (8.7)	0	0	0
General disorders and administration site conditions				
Injection site erythema	1 (4.3)	2 (9.5)	11 (16.7)	13 (14.9)
Fatigue	4 (17.4)	2 (9.5)	6 (9.1)	8 (9.2)
Injection site discolouration	1 (4.3)	1 (4.8)	7 (10.6)	8 (9.2)
Pyrexia	0	2 (9.5)	5 (7.6)	7 (8.0)
Chills	0	1 (4.8)	5 (7.6)	6 (6.9)
Injection site pain	0	2 (9.5)	3 (4.5)	5 (5.7)
Injection site swelling	0	0	4 (6.1)	4 (4.6)
Musculoskeletal and connective tissue disorders				
Arthralgia	0	4 (19.0	5 (7.6)	9 (10.3)
Pain in extremity	1 (4.3)	2 (9.5)	5 (7.6)	7 (8.0)
Myalgia	0	0	6 (9.1)	6 (6.9)
Back pain	2 (8.7)	0	5 (7.6)	5 (5.7)
Respiratory, thoracic and mediastinal disorders				
Cough	2 (8.7)	3 (14.3)	6 (9.1)	9 (10.3)

System Organ Class Preferred Term	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Oropharyngeal pain	0	1 (4.8)	8 (12.1)	9 (10.3)
Epistaxis	1 (4.3)	2 (9.5)	0	2 (2.3)
Nervous system disorders				
Headache	3 (13.0)	4 (19.0)	8 (12.1)	12 (13.8)
Migraine	2 (8.7)	1 (4.8)	1 (1.5)	2 (2.3)
Metabolism and nutrition disorders				
Type 2 diabetes mellitus	1 (4.3)	2 (9.5)	2 (3.0)	4 (4.6)
Hypoglycaemia	2 (8.7)	1 (4.8)	2 (3.0)	3 (3.4)
Hyponatraemia	2 (8.7)	0	0	0
Injury, poisoning and procedural complications				
Arthropod bite	0	2 (9.5)	0	2 (2.3)
Ligament sprain	0	2 (9.5)	0	2 (2.3)
Skin laceration	2 (8.7)	1 (4.8)	1 (1.5)	2 (2.3)
Psychiatric disorders				
Anxiety	0	4 (19.0)	0	4 (4.6)
Renal and urinary disorders				
Dysuria	0	2 (9.5)	0	2 (2.3)
Proteinuria	2 (8.7)	0	1 (1.5)	1 (1.1)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For patients who received olezarsen in the index study CS3, all AEs collected in CS13 were considered as TEAE. For patients who received placebo in CS3 and rolled over to CS13, the TEAEs for the CS3 placebo period were defined as any adverse event starting or worsening on or after receiving the first dose of placebo in CS3 and before the first dose of olezarsen in CS13. TEAEs in CS13 were defined as any adverse event starting or worsening on or after receiving the first dose of olezarsen in CS13.
Note: Adverse events were coded using MedDRA Version 26.0.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The ISIS 678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS 678354 80 mg and then had their dose reduced to 50 mg.
Note: Percentages are rounded to one decimal place; however, actual values were used to determine the > 5.0% cutoff (e.g., value may be rounded down to 5.0%, but actual value is 5.02, which is > 5.0%).
Abbreviations: AE = adverse event; FCS = familial chylomicronemia syndrome; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

In Pool 4, 39.1% of patients in placebo group had at least one severe AE, comparing with 7.6% and 9.2% in olezarsen 80 mg group and total olezarsen group, respectively.

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Overall in Pool 5, number of patients who experienced TEAEs was similar in the placebo group (83.7%) compared with the olezarsen 80 mg group (78.0%).

In the olezarsen 80 mg group, the most frequently experienced TEAEs were COVID-19 and abdominal pain (13.8% each); injection site erythema (10.6%); headache (8.1%); cough (7.3%); nausea and oropharyngeal pain (6.5% each); and nasopharyngitis, influenza, pain in extremity, fatigue, injection site discolouration, and vomiting (5.7% each). Of these TEAEs, abdominal pain, injection site erythema, headache, cough, nausea, oropharyngeal pain, pain in extremity, injection site

discolouration, and vomiting were more frequently experienced in the olezarsen 80 mg group than in the placebo group.

In Pool 5, 15.1% of patients in placebo group had at least one severe AE, comparing with 6.5% in olezarsen 80 mg group.

Adverse drug reactions

Pool 1

Table 37: ADRs by System Organ Class and Preferred Term (CS3, CS8, and Pool 1)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with at least one related TEAE, n (%)	5 (21.7)	6 (28.6)	7 (31.8)	13 (30.2)	3 (7.7)	16 (27.6)	8 (14.0)	24 (20.9)	8 (12.0)	22 (27.9)	15 (19.5)	37 (23.7)
General disorders and administration site conditions												
Injection site erythema	1 (4.3)	1 (4.8)	1 (4.5)	2 (4.7)	0	7 (12.1)	2 (3.5)	9 (7.8)	1 (1.3)	8 (9.8)	3 (3.8)	11 (6.9)
Fatigue	0	1 (4.8)	0	1 (2.3)	0	2 (3.4)	1 (1.8)	3 (2.6)	0	3 (3.9)	1 (1.2)	4 (2.5)
Injection site pain	0	2 (9.5)	1 (4.5)	3 (7.0)	0	1 (1.7)	0	1 (0.9)	0	3 (4.1)	1 (1.4)	4 (2.7)
Injection site discolouration	1 (4.3)	1 (4.8)	0	1 (2.3)	0	2 (3.4)	0	2 (1.7)	1 (1.3)	3 (3.9)	0	3 (1.9)
Chills	0	1 (4.8)	1 (4.5)	2 (4.7)	0	0	0	0	0	1 (1.5)	1 (1.4)	2 (1.4)
Injection site pruritus	0	1 (4.8)	0	1 (2.3)	1 (2.6)	1 (1.7)	0	1 (0.9)	1 (1.8)	2 (2.7)	0	2 (1.3)
Chest discomfort	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Injection site bruising	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Injection site haemorrhage	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Injection site inflammation	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Injection site reaction	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Injection site urticaria	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Peripheral swelling	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Asthenia	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Investigations												
Platelet count decreased	1 (4.3)	1 (4.8)	3 (13.6)	4 (9.3)	0	0	1 (1.8)	1 (0.9)	1 (1.3)	1 (1.5)	4 (5.4)	5 (3.5)
Gamma-glutamyl transferase increased	1 (4.3)	1 (4.8)	0	1 (2.3)	0	1 (1.7)	1 (1.8)	2 (1.7)	1 (1.3)	2 (2.7)	1 (1.2)	3 (1.9)
Alanine aminotransferase increased	0	0	0	0	0	1 (1.7)	1 (1.8)	2 (1.7)	0	1 (1.2)	1 (1.2)	2 (1.2)
Aspartate aminotransferase increased	0	0	0	0	0	1 (1.7)	1 (1.8)	2 (1.7)	0	1 (1.2)	1 (1.2)	2 (1.2)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Liver function test increased	0	0	0	0	0	2 (3.4)	0	2 (1.7)	0	2 (2.4)	0	2 (1.2)
Albumin urine present	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Blood creatinine increased	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Glomerular filtration rate decreased	0	0	0	0	1 (2.6)	1 (1.7)	0	1 (0.9)	1 (1.8)	1 (1.2)	0	1 (0.6)
Urine protein/creatinine ratio abnormal	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Urine protein/creatinine ratio increased	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Gastrointestinal disorders												
Diarrhoea	0	1 (4.8)	1 (4.5)	2 (4.7)	0	0	0	0	0	1 (1.5)	1 (1.4)	2 (1.4)
Abdominal pain lower	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Nausea	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)
Salivary hypersecretion	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)
Vomiting	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Vascular disorders												
Flushing	0	1 (4.8)	1 (4.5)	2 (4.7)	0	0	1 (1.8)	1 (0.9)	0	1 (1.5)	2 (2.6)	3 (2.0)
Musculoskeletal and connective tissue disorders												
Pain in extremity	0	0	2 (9.1)	2 (4.7)	0	0	0	0	0	0	2 (2.8)	2 (1.4)
Arthralgia	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Myalgia	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Trismus	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Ear and labyrinth disorders												
Ear pain	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Nervous system disorders												
Headache	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Renal and urinary disorders												
Proteinuria	2 (8.7)	0	0	0	0	1 (1.7)	0	1 (0.9)	2 (2.7)	1 (1.2)	0	1 (0.6)
Skin and subcutaneous tissue disorders												
Alopecia	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Hyperhidrosis	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8).
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of study drug.
Note: Related was defined as "Related", "Possible", "Possibly Related", or missing relationship to study drug.
Note: For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.
Note: Adverse events were coded using MedDRA Version 26.0.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

In Pool 1, in olezarsen treatment groups, all ADRs were mild or moderate in severity. In the placebo group, 2 patients experienced an ADR that was considered severe.

Pool 4 (CS3 + CS13 + CS7)

Table 38: ADRs by System Organ Class and Preferred Term (Pool 4)

System Organ Class Preferred Term	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Patients with at least one related TEAE, n (%)	5 (21.7)	8 (38.1)	31 (47.0)	39 (44.8)
General disorders and administration site conditions				
Injection site erythema	1 (4.3)	2 (9.5)	10 (15.2)	12 (13.8)
Injection site discolouration	1 (4.3)	1 (4.8)	7 (10.6)	8 (9.2)
Chills	0	1 (4.8)	4 (6.1)	5 (5.7)
Injection site pain	0	2 (9.5)	2 (3.0)	4 (4.6)
Injection site swelling	0	0	4 (6.1)	4 (4.6)
Fatigue	0	2 (9.5)	1 (1.5)	3 (3.4)
Injection site inflammation	0	0	2 (3.0)	2 (2.3)
Injection site pruritus	0	1 (4.8)	1 (1.5)	2 (2.3)
Injection site urticaria	0	0	2 (3.0)	2 (2.3)
Asthenia	1 (4.3)	0	1 (1.5)	1 (1.1)
Chest discomfort	0	0	1 (1.5)	1 (1.1)
Injection site haematoma	0	0	1 (1.5)	1 (1.1)
Injection site hypoaesthesia	0	0	1 (1.5)	1 (1.1)
Injection site oedema	0	0	1 (1.5)	1 (1.1)
Injection site papule	0	1 (4.8)	0	1 (1.1)

System Organ Class Preferred Term	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Injection site paraesthesia	0	0	1 (1.5)	1 (1.1)
Injection site reaction	0	0	1 (1.5)	1 (1.1)
Pain	0	0	1 (1.5)	1 (1.1)
Peripheral swelling	0	0	1 (1.5)	1 (1.1)
Thirst	0	0	1 (1.5)	1 (1.1)
Gastrointestinal disorders				
Vomiting	0	0	3 (4.5)	3 (3.4)
Diarrhoea	0	1 (4.8)	1 (1.5)	2 (2.3)
Nausea	0	1 (4.8)	1 (1.5)	2 (2.3)
Abdominal discomfort	0	0	1 (1.5)	1 (1.1)
Abdominal distension	0	0	1 (1.5)	1 (1.1)
Abdominal pain lower	0	0	1 (1.5)	1 (1.1)
Pancreatitis	0	0	1 (1.5)	1 (1.1)
Salivary hypersecretion	0	1 (4.8)	0	1 (1.1)
Investigations				
Platelet count decreased	1 (4.3)	1 (4.8)	3 (4.5)	4 (4.6)
Albumin urine present	0	0	1 (1.5)	1 (1.1)
Blood cholesterol increased	0	0	1 (1.5)	1 (1.1)
Blood triglycerides increased	0	0	1 (1.5)	1 (1.1)
Gamma-glutamyltransferase increased	1 (4.3)	1 (4.8)	0	1 (1.1)
Glomerular filtration rate decreased	0	0	1 (1.5)	1 (1.1)
Hepatic enzyme increased	0	0	1 (1.5)	1 (1.1)

System Organ Class Preferred Term	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Non-high-density lipoprotein cholesterol increased	0	0	1 (1.5)	1 (1.1)
Urine protein/creatinine ratio increased	0	0	1 (1.5)	1 (1.1)
Musculoskeletal and connective tissue disorders				
Myalgia	0	0	5 (7.6)	5 (5.7)
Arthralgia	0	1 (4.8)	2 (3.0)	3 (3.4)
Pain in extremity	0	1 (4.8)	2 (3.0)	3 (3.4)
Muscle fatigue	0	1 (4.8)	0	1 (1.1)
Trismus	0	0	1 (1.5)	1 (1.1)
Nervous system disorders				
Headache	0	2 (9.5)	3 (4.5)	5 (5.7)
Dizziness	0	0	1 (1.5)	1 (1.1)
Migraine	0	0	1 (1.5)	1 (1.1)
Paraesthesia	0	0	1 (1.5)	1 (1.1)
Immune system disorders				
Hypersensitivity	0	0	2 (3.0)	2 (2.3)
Anaphylactic reaction	0	0	1 (1.5)	1 (1.1)
Vascular disorders				
Flushing	0	1 (4.8)	1 (1.5)	2 (2.3)
Infections and infestations				
Influenza	0	0	1 (1.5)	1 (1.1)
Injury, poisoning and procedural complications				

System Organ Class Preferred Term	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
Injection related reaction	0	1 (4.8)	0	1 (1.1)
Metabolism and nutrition disorders				
Decreased appetite	0	0	1 (1.5)	1 (1.1)
Psychiatric disorders				
Insomnia	0	0	1 (1.5)	1 (1.1)
Skin and subcutaneous tissue disorders				
Alopecia	0	0	1 (1.5)	1 (1.1)
Renal and urinary disorders				
Proteinuria	2 (8.7)	0	0	0

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For patients who received olezarsen in the index study CS3, all AEs collected in CS13 were considered as TEAE. For patients who received placebo in CS3 and rolled over to CS13, the TEAEs for the CS3 placebo period were defined as any adverse event starting or worsening on or after receiving the first dose of placebo in CS3 and before the first dose of olezarsen in CS13. TEAEs in CS13 were defined as any adverse event starting or worsening on or after receiving the first dose of olezarsen in CS13.
Note: Adverse events were coded using MedDRA Version 26.0.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The ISIS 678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS 678354 80 mg and then had their dose reduced to 50 mg.
Abbreviations: AE = adverse event; FCS = familial chylomicronemia syndrome;
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Pool 4: ADRs by Severity

Across all FCS population studies, 2 patients in the placebo group (8.7%) and 2 patients in the olezarsen 80 mg group (3.0%) experienced severe ADrs; no patient in the olezarsen 50 mg/80 mg group experienced severe ADRs.

According to the pooled safety analysis, the most common ADRs in olezarsen 80 mg group are injection site reactions, such as Injection site erythema, Injection site discolouration, Injection site pain and Injection site swelling, also Vomiting, Myalgia, Headache and Hypersensitivity. They were more frequent

in olezarsen 80 mg group comparing with placebo group in Pool 4 and Pool 5. The number of severe ADRs was similar in olezarsen 80 mg group and placebo group and low in general.

2.5.8.3. Serious adverse event/deaths/other significant events

Pool 1 (CS3+CS8)

Table 39: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (CS3, CS8, and Pool 1

	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
System Organ Class Preferred Term	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with at least one serious TEAE, n (%)	9 (39.1)	4 (19.0)	3 (13.6)	7 (16.3)	2 (5.1)	6 (10.3)	8 (14.0)	14 (12.2)	11 (15.6)	10 (13.0)	11 (13.9)	21 (13.4)
Cardiac disorders												
Acute myocardial infarction	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Angina pectoris	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Atrial fibrillation	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Coronary artery disease	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Left ventricular failure	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Tachycardia	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Gastrointestinal disorders												
Pancreatitis	4 (17.4)	1 (4.8)	1 (4.5)	2 (4.7)	0	0	0	0	4 (5.3)	1 (1.5)	1 (1.4)	2 (1.4)
Intestinal perforation	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Pancreatitis acute	3 (13.0)	0	0	0	0	1 (1.7)	0	1 (0.9)	3 (4.0)	1 (1.2)	0	1 (0.6)
Small intestinal obstruction	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Gastric varices	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Gastric varices haemorrhage	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Gastritis	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Pancreatitis necrotising	2 (8.7)	0	0	0	0	0	0	0	2 (2.7)	0	0	0

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Invasive ductal breast carcinoma	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Non-Hodgkin's lymphoma	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Rectal cancer	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Squamous cell carcinoma of head and neck	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Endometrial cancer stage I	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Squamous cell carcinoma of the oral cavity	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
General disorders and administration site conditions												
Death	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Drug withdrawal syndrome	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Sudden death	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)
Infections and infestations												
Sepsis	0	0	0	0	0	1 (1.7)	1 (1.8)	2 (1.7)	0	1 (1.2)	1 (1.2)	2 (1.2)
Cellulitis	1 (4.3)	0	0	0	0	0	1 (1.8)	1 (0.9)	1 (1.3)	0	1 (1.2)	1 (0.6)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Gastroenteritis bacterial	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)
Injury, poisoning and procedural complications												
Intentional overdose	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)
Tibia fracture	0	0	0	0	1 (2.6)	0	1 (1.8)	1 (0.9)	1 (1.8)	0	1 (1.2)	1 (0.6)
Head injury	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Ligament sprain	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Nervous system disorders												
Encephalopathy	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Lacunar infarction	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Syncope	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Hepatobiliary disorders												
Hepatic cirrhosis	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Cholangitis	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Metabolism and nutrition disorders												
Hypoglycaemia	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Hyponatraemia	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Pancreatogenous diabetes	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8).
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug.
Note: For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.
Note: AEs were classified according to MedDRA Version 26.0.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Pool 4 (CS3 + CS13 + CS7)

Across all FCS population studies, a lower proportion of patients in the olezarsen 80 mg group (16.7%) experienced serious TEAEs compared with the olezarsen 50 mg/80 mg group (23.8%) and the placebo group (39.1%).

Table 40: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Set – Pool 4 (CS3, CS7, and CS13)

System Organ Class/ Preferred Term	Placebo (N=23) n (%) Events	Olezarsen 50 mg/80 mg (N = 21) n (%) Events	Olezarsen 80 mg (N = 66) n (%) Events	Total Olezarsen (N = 87) n (%) Events
Patients with any Serious TEAEs	***9 (39.1) 21***	***5 (23.8) 5***	***11 (16.7) 19***	***16 (18.4) 24***
Gastrointestinal disorders	**9 (39.1) 15**	**1 (4.8) 1**	**6 (9.1) 11**	**7 (8.0) 12**
Pancreatitis	4 (17.4) 5	1 (4.8) 1	4 (6.1) 6	5 (5.7) 7
Haematemesis	0	0	1 (1.5) 1	1 (1.1) 1
Intestinal perforation	0	0	1 (1.5) 2	1 (1.1) 2
Lower gastrointestinal haemorrhage	0	0	1 (1.5) 1	1 (1.1) 1
Umbilical hernia	0	0	1 (1.5) 1	1 (1.1) 1
Gastric varices	1 (4.3) 1	0	0	0
Gastric varices haemorrhage	1 (4.3) 1	0	0	0
Gastritis	1 (4.3) 1	0	0	0
Pancreatitis acute	3 (13.0) 5	0	0	0
Pancreatitis necrotising	2 (8.7) 2	0	0	0
Immune system disorders	**0**	**0**	**3 (4.5) 3**	**3 (3.4) 3**
Hypersensitivity	0	0	2 (3.0) 2	2 (2.3) 2
Anaphylactic reaction	0	0	1 (1.5) 1	1 (1.1) 1
General disorders and administration site conditions	**0**	**1 (4.8) 1**	**1 (1.5) 1**	**2 (2.3) 2**
Discharge	0	0	1 (1.5) 1	1 (1.1) 1
Sudden death	0	1 (4.8) 1	0	1 (1.1) 1
Hepatobiliary disorders	**1 (4.3) 1**	**0**	**2 (3.0) 3**	**2 (2.3) 3**
Cholangitis	1 (4.3) 1	0	1 (1.5) 2	1 (1.1) 2
Hepatic cirrhosis	0	0	1 (1.5) 1	1 (1.1) 1
Cardiac disorders	**0**	**0**	**1 (1.5) 1**	**1 (1.1) 1**
Hypertensive heart disease	0	0	1 (1.5) 1	1 (1.1) 1
Endocrine disorders	**0**	**1 (4.8) 1**	**0**	**1 (1.1) 1**
Thyroid mass	0	1 (4.8) 1	0	1 (1.1) 1

Infections and infestations	**1 (4.3) 1**	**1 (4.8) 1**	**0**	**1 (1.1) 1**
Gastroenteritis bacterial	0	1 (4.8) 1	0	1 (1.1) 1
Cellulitis	1 (4.3) 1	0	0	0
Injury, poisoning and procedural complications	**0**	**1 (4.8) 1**	**0**	**1 (1.1) 1**
Intentional overdose	0	1 (4.8) 1	0	1 (1.1) 1
Metabolism and nutrition disorders	**2 (8.7) 3**	**0**	**0**	**0**
Hypoglycaemia	1 (4.3) 1	0	0	0
Hyponatraemia	1 (4.3) 1	0	0	0
Pancreatogenous diabetes	1 (4.3) 1	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (4.3) 1**	**0**	**0**	**0**
Squamous cell carcinoma of the oral cavity	1 (4.3) 1	0	0	0

Patients took placebo in CS3 then took olezarsen in CS13 were included in both placebo and active treatment groups.
N = number of safety patients in treatment group; n = number of patients in the specified category; %=n/N*100.
A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For patients who received olezarsen in the index study CS3, all AEs collected in CS13 were considered as TEAE. For patients who received placebo in CS3 and rolled over to CS13, the TEAEs for the CS3 placebo period were defined as any adverse event starting or worsening on or after receiving the first dose of placebo in CS3 and before the first dose of olezarsen in CS13. TEAEs in CS13 were defined as any adverse event starting or worsening on or after receiving the first dose of olezarsen in CS13.
For the summarization of number of patients (n), a patient was counted only once even if reported one or more events. A patient was classified according to the worst reported severity if the patient reported one or more events. For each summarization level of number of events, all TEAEs were counted.
The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
The ISIS 678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS 678354 80 mg and then had their dose reduced to 50 mg.
MedDRA version 26.0 was applied.

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Overall, a similar proportion of patients experienced serious TEAEs across all treatment groups. Specifically regarding olezarsen 80 mg group, 15.4% of patients experienced at least 1 SAE, compared with 15.1% in the placebo group.

2.5.8.3.1. Deaths

Across all phase 2 and phase 3 studies, 3 (1.0%) patients experienced a serious TEAE leading to death, 1 patient in the olezarsen 50 mg group in Study CS3 (AE of sudden death, unknown cause; determined as MACE by MACE adjudication committee), 1 in the olezarsen 50 mg group of Study CS8 (unknown cause) and 1 patient in the olezarsen 15 mg every 2 weeks group in Study CS2 (cardiac arrest). All events were assessed as not related or unlikely related to olezarsen. No patients that received olezarsen 80 mg experienced a serious TEAE leading to death.

2.5.8.3.2. AEs of special interest

Overall across all 5 studies, no patient experienced an AESI 1, defined as severe reductions in platelet count (< 50,000/mm3) accompanied by a major bleeding event or clinically relevant non-major

bleeding event, or platelet count of < 25,000/mm3 independent of a major bleeding or clinically relevant non-major bleeding event.

Overall across all 5 studies, 1 patient in study CS13 experienced an AESI 2, defined as requirement of any use of medications (prophylactic treatment, such as antihistamines, acetaminophen, non-steroidal anti-inflammatory drugs, corticosteroids, etc.) as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction. It was assessed as severe SAE of anaphylactic reaction by the investigator.

2.5.8.3.3. Other AEs of Interest

Injection Site Reactions (ISR)

Pool 1 (CS3 + CS8)

In Pool 1, number of patients with at least one ISR was smaller in placebo group, compared with olezarsen: 2.7% vs 7.8% in olezarsen 80 mg group and 12.1% in total olezarsen group. Then most common in olezarsen 80 mg group were Injection site erythema and Injection site bruising.

Pool 4 (CS3 + CS13 + CS7)

In the olezarsen 80 mg group, 11 (16.7%) patients experienced at least 1 ISR, for a median (range) duration of 8 (0 to 294) days, after a median (range) of 2 (1 to 16) injections.

In the placebo group, 2 (8.7%) patients experienced at least 1 ISR, for a median (range) duration of 133 (8 to 258) days, after a median (range) of 3 (2 to 4) injections.

Overall, the time to onset of the first post-Baseline ISR in the different groups ranged from 1 to 421 days.

Table 41: Injection Site Reactions (ISR) by Preferred Term Safety Set – Pool 4

Preferred Term	**Placebo (N=23) n (%)**	**Olezarsen 50mg/80mg (N=21) n (%)**	**Olezarsen 80mg (N=66) n (%)**	**Total Olezarsen (N=87) n (%)**
Patients with any ISRs	***2 (8.7)***	***4 (19.0)***	***11 (16.7)***	***15 (17.2)***
Injection site erythema	1 (4.3)	2 (9.5)	7 (10.6)	9 (10.3)
Injection site discolouration	1 (4.3)	1 (4.8)	4 (6.1)	5 (5.7)
Injection site pain	0	1 (4.8)	2 (3.0)	3 (3.4)
Injection site swelling	0	0	3 (4.5)	3 (3.4)
Injection site bruising	0	0	1 (1.5)	1 (1.1)
Injection site haematoma	0	0	1 (1.5)	1 (1.1)
Injection site inflammation	0	0	1 (1.5)	1 (1.1)
Injection site oedema	0	0	1 (1.5)	1 (1.1)

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Overall, a lower proportion of patients in the placebo group (3.5%) experienced ISRs compared with the olezarsen 80 mg group (11.4%), the olezarsen 50 mg/80 mg group (14.9%), and the olezarsen 10-40 mg group (14.7%).

There were no serious or severe ISRs. There was 1 dose reduction in 1 patient in the olezarsen 80 mg group and 8 OAEIs of ISR leading to permanent discontinuation in 4 patients in the olezarsen 50 mg group from study CS8 following OAEI of ISR.

In the olezarsen 80 mg group, experienced ISRs were injection site erythema, injection site discolouration, injection site pain, injection site swelling, injection site bruising, injection site oedema, injection site haematoma, and injection site inflammation, for a median (range) duration of 8 (0 to 424) days, after a median (range) of 2 (1 to 3) injections.

Local Cutaneous Reactions at the Injection Site (LCRIS)

Pool 1 (CS3 + CS8)

Overall in Pool 1, 4 (4.8%) patients in the olezarsen 50 mg group discontinued study drug as a result of OAEI of LCRIS per definition B. Patients experienced these events for a median (range) duration of 80 (9 to 311) days, after a median (range) of 2.5 (1 to 6) injections. There were no serious or severe LCRIS. The time to onset of the first post-Baseline LCRIS in the different treatment groups ranged from 24 to 143 days.

Pool 4 (CS3 + CS13 + CS7)

Across all FCS population studies, 1 (1.5%) patient in the olezarsen 80 mg group experienced OAEI of LCRIS per definition A (injection site erythema, injection site pain, and injection site swelling), for a duration of 4 days, after 8 injections. There were no LCRIS per definition B. There were no serious or severe LCRIS and no dose change of study drug, or discontinuation from the study, following OAEI of LCRIS. The time to onset of the first LCRIS in the patient from the olezarsen 80 mg group was 196.0 days.

Flu-like reactions (FLR)

Pool 1 (CS3 + CS8)

No patient in any treatment group experienced a FLR2. FLR1 were experienced by 1 (1.4%) patient in olezarsen 80 mg group and by 2 (1.4%) patients in total olezarsen group, compared with none in placebo group.

Pool 4 (CS3 + CS13 + CS7)

Across all FCS population studies, 7 (10.6%) patients in the olezarsen 80 mg group experienced FLR 1 (arthralgia, chills, and myalgia); 1 (4.8%) patient in the olezarsen 50 mg group experienced FLR 1 (chills); no patient in the placebo group experienced FLR 1. No patients in any treatment group experienced an OAEI of flu-like reaction according to FLR 2 in this pool.

There were no serious or severe FLR; 1 patient in the olezarsen 80 mg group permanently discontinued the study treatment due to moderate FLR TEAEs after dose reduction.

Overall, the time to onset of the first post-Baseline FLR 1 ranged between 1 and 428 days, after a number of injections ranging from 1 to 15 injections.

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Overall, OAEIs of flu-like reaction that met the criteria for FLR 1 were experienced by 7 (5.7%) patients in the olezarsen 80 mg group (arthralgia, chills, and myalgia), by 2 (2.0%) patients in the olezarsen 50 mg/80 mg group (arthralgia and chills), by 7 (10.3%) patients in the olezarsen 10-40 mg group (influenza like illness, arthralgia, and myalgia), and by 2 (2.3%) patients in the placebo group (myalgia). OAEI of flu-like reaction that met the criteria for FLR 2 was experienced by 1 (1.5%) patient in the olezarsen 10-40 mg group (influenza like illness).

There were no serious or severe FLR; 1 patient in the olezarsen 80 mg group permanently discontinued the study treatment due to moderate FLR TEAEs after dose reduction.

Overall, the time to onset of the first post-baseline FLR 1 ranged between 1 and 428 days, after a number of injections ranging from 1 to 40 injections.

Bleeding Adverse events

Pool 1 (CS3 + CS8)

Table 42: Bleeding Treatment-Emergent Adverse Events by SMQ (Broad and Narrow) and System Organ Class and Preferred Term (CS3, CS8, and Pool 1)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with At Least One Bleeding TEAE, n (%)	4 (17.4)	3 (14.3)	4 (18.2)	7 (16.3)	2 (5.1)	3 (5.2)	3 (5.3)	6 (5.2)	6 (8.9)	6 (8.0)	7 (9.2)	13 (8.6)
General disorders and administration site conditions												
Injection site bruising	0	0	1 (4.5)	1 (2.3)	0	0	1 (1.8)	1 (0.9)	0	0	2 (2.6)	2 (1.3)
Injection site haemorrhage	0	0	0	0	0	2 (3.4)	0	2 (1.7)	0	2 (2.4)	0	2 (1.2)
Investigations												
Haematocrit decreased	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Haemoglobin decreased	1 (4.3)	0	1 (4.5)	1 (2.3)	0	0	0	0	1 (1.3)	0	1 (1.4)	1 (0.7)
International normalized ratio increased	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Injury, poisoning and procedural complications												
Bone contusion	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Contusion	0	1 (4.8)	1 (4.5)	2 (4.7)	1 (2.6)	0	0	0	1 (1.8)	1 (1.5)	1 (1.4)	2 (1.4)
Eye contusion	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Gastrointestinal disorders												

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Gastric varices haemorrhage	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Haematemesis	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Haematochezia	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Renal and urinary disorders												
Haematuria	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Respiratory, thoracic and mediastinal disorders												
Epistaxis	1 (4.3)	2 (9.5)	0	2 (4.7)	0	0	1 (1.8)	1 (0.9)	1 (1.3)	2 (2.9)	1 (1.2)	3 (2.0)
Vascular disorders												
Haematoma	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: For the summarization of number of patients (n), a patient was counted only once for each System Organ Class and Preferred Term even if > 1 event was reported.
Note: Bleeding AEs were identified based on the Haemorrhages (SMQ [broad and narrow]) exported from MedDRA Version 26.0.

Pool 4 (CS3 + CS13 + CS7)

The majority of the bleeding TEAEs in Pool 4, including clinical bleeding TEAEs, were non-serious and mild or moderate in severity, unlikely related or not related to the study drug, and did not lead to study drug discontinuation or interruption. Serious bleeding TEAEs were reported in 3 patients, including 2 patients from the olezarsen 80 mg group (1 patient with severe SAE lower gastrointestinal haemorrhage, 1 patient with mild SAE haematemesis), and 1 patient in the placebo group (severe SAE gastric varices haemorrhage leading to study drug interruption); none of these patients had platelet counts below normal within 2 weeks prior to the serious bleeding events.

The proportion of patients experiencing clinical bleeding TEAEs with concomitant anticoagulant or antiplatelet medication was greater in the placebo group (2 [8.7%] patients; TEAEs of gastric varices haemorrhage and epistaxis) compared with the olezarsen 80 mg group (2 [3.0%] patients; TEAEs of haematochezia and lower gastrointestinal haemorrhage); no patients in the olezarsen 50 mg/80 mg group experienced a clinical bleeding TEAE with concomitant anticoagulant or antiplatelet medication.

Table 43: Bleeding Treatment-Emergent Adverse Events by SMQ (Broad and Narrow) and System Organ Class and Preferred Term Safety Set – Pool 4

SMQ **System Organ Class** **Preferred Term**	**Placebo (N=23)** **n (%)**Events	**Olezarsen 50mg/80mg (N=21)** **n (%)**Events	**Olezarsen 80mg (N=66)** **n (%)** Events	**Total Olezarsen (N=87)** **n (%)** Events
Patients with any Bleeding TEAE	***4 (17.4) 4***	***3 (14.3) 3***	***8 (12.1) 14***	***11 (12.6) 17***
Gastrointestinal disorders	**2 (8.7) 2**	**0**	**4 (6.1) 5**	**4 (4.6) 5**
Haematemesis	1 (4.3) 1	0	1 (1.5) 1	1 (1.1) 1
Haematochezia	0	0	1 (1.5) 1	1 (1.1) 1
Haemorrhoidal haemorrhage	0	0	1 (1.5) 1	1 (1.1) 1
Lower gastrointestinal haemorrhage	0	0	1 (1.5) 1	1 (1.1) 2
Gastric varices haemorrhage	1 (4.3) 1	0	0	0
General disorders and administration site conditions	**0**	**0**	**2 (3.0) 6**	**2 (2.3) 6**
Injection site bruising	0	0	1 (1.5) 2	1 (1.1) 2
Injection site haematoma	0	0	1 (1.5) 4	1 (1.1) 4
Injury, poisoning and procedural complications	**0**	**1 (4.8) 1**	**1 (1.5) 1**	**2 (2.3) 2**
Contusion	0	1 (4.8) 1	1 (1.5) 1	2 (2.3) 2
Respiratory, thoracic and mediastinal disorders	**1 (4.3) 1**	**2 (9.5) 2**	**0**	**2 (2.3) 2**
Epistaxis	1 (4.3) 1	2 (9.5) 2	0	2 (2.3) 2
Investigations	**1 (4.3) 1**	**0**	**1 (1.5) 2**	**1 (1.1) 2**
Haematocrit decreased	0	0	1 (1.5) 1	1 (1.1) 1

Haemoglobin decreased	1 (4.3) 1	0	1 (1.5) 1	1 (1.1) 1

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

The proportion of patients who experienced bleeding TEAEs in Pool 5 was slightly lower in the olezarsen 80 mg group (11 patients [8.9%]) and olezarsen 50 mg/80 mg group (11 patients [10.9%]), compared with the olezarsen 10-40 group (10 patients [14.7%]) and the placebo group (12 patients [14.0%]).

The proportion of patients with clinical bleeding TEAEs in the olezarsen 80 mg group (7 patients [5.7%]) was slightly lower compared with the placebo group (9 patients [10.5%]), and similar to the olezarsen 50 mg/80 mg group (8 patients [7.9%]), and the olezarsen 10-40 mg group (5 patients [7.4%]).

The majority of the bleeding TEAEs, including clinical bleeding TEAEs were non-serious, mild or moderate in severity, not related or unlikely related to the study drug, and did not lead to study drug discontinuation or interruption. Serious clinical bleeding TEAEs were reported in 4 patients, including 2 patients from the olezarsen 80 mg group (1 patient with severe SAE lower gastrointestinal haemorrhage, 1 patient with SAE haematemesis [mild]), and 2 patients from the placebo group (1 patient with SAE Henoch Schonlein purpura [severe], and 1 patient with SAE gastric varices haemorrhage [severe] leading to study drug interruption). Two (2) non-serious bleeding TEAE of Injection site haemorrhage (1 mild, 1 moderate) leading to study drug discontinuation were reported in 2 patients in the olezarsen 50 mg group.

Thrombocytopenia Adverse Events

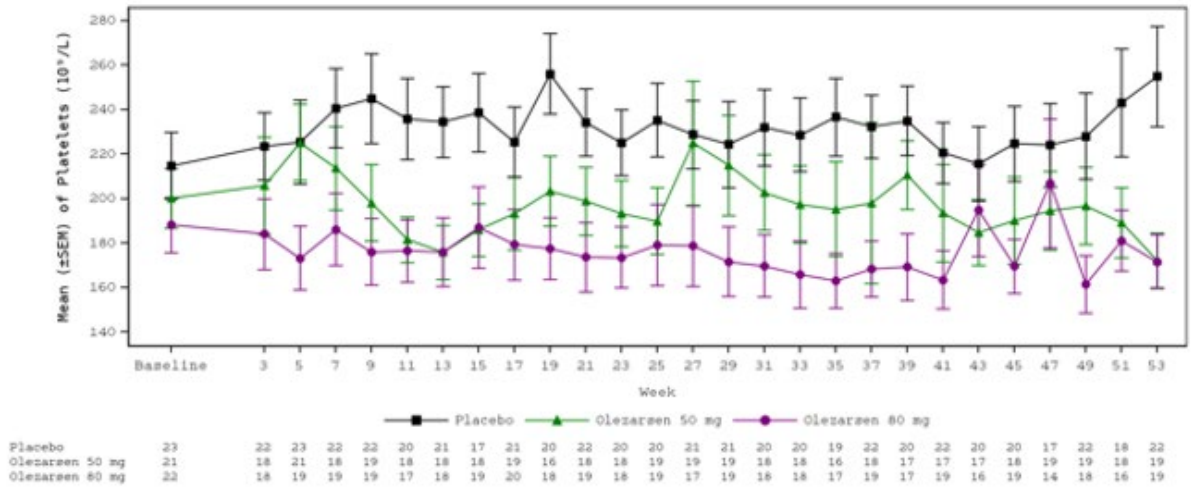
Study CS3

The proportion of patients with thrombocytopenia TEAEs was higher in the olezarsen 80 mg and the olezarsen 50 mg groups compared with the placebo group (details provided in the table under "Pool 1" below); of note, the absolute number of patients with thrombocytopenia TEAEs is low, with a disproportionate percentage difference driven by the relatively small cohort sizes.

Most thrombocytopenia TEAEs were mild in severity, and there were no severe thrombocytopenia TEAEs. None of the patients with thrombocytopenia TEAEs experienced concurrent clinical bleeding events, met the predefined stopping rule regarding platelet counts or discontinued treatment due to the thrombocytopenia TEAE.

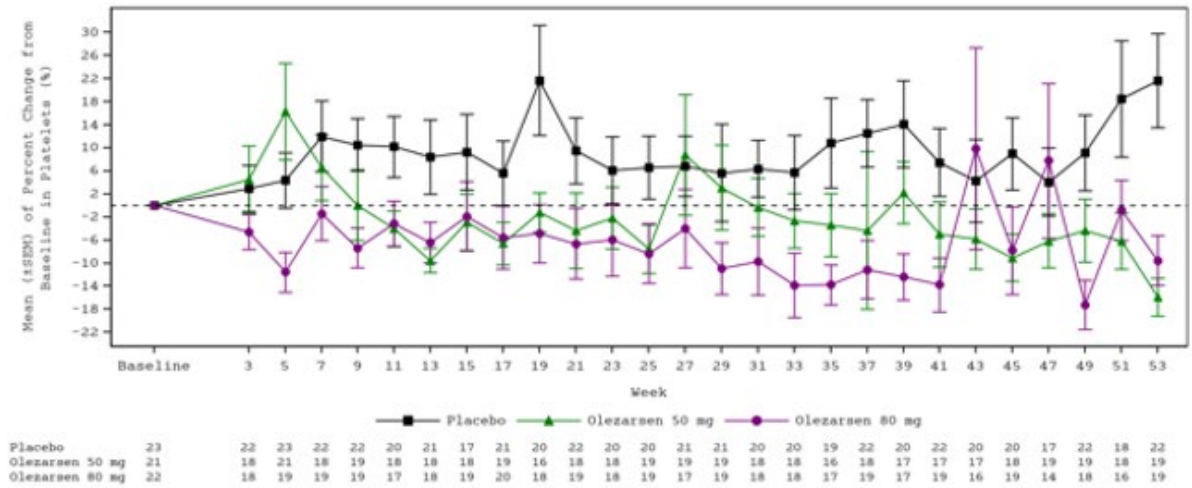
For all treatment groups, the mean percent changes from Baseline in platelet counts over time were variable through the treatment period. The mean platelet counts in the olezarsen 80 mg group were lower at Baseline compared with the olezarsen 50 mg group and the placebo group. The mean platelet counts remained within the reference range and the observed changes over time were not clinically meaningful. Mean platelet values and mean percent change from Baseline in platelet count over time are presented for all treatment groups in Figure 12 below.

Mean (±SEM) Platelet Count (10^9/L)



Placebo	23	22	23	22	22	20	21	17	21	20	22	20	20	21	21	20	20	19	22	20	22	20	20	17	22	18	22
Olezarsen 50 mg	21	18	21	18	19	18	18	18	19	16	18	18	19	19	19	18	18	16	18	17	17	17	18	19	19	18	19
Olezarsen 80 mg	22	18	19	19	19	17	18	19	20	18	19	18	19	17	19	18	18	17	19	17	19	16	19	14	18	16	19

Mean (±SEM) Percent Change from Baseline



Placebo	23	22	23	22	22	20	21	17	21	20	22	20	20	21	21	20	20	19	22	20	22	20	20	17	22	18	22
Olezarsen 50 mg	21	18	21	18	19	18	18	18	19	16	18	18	19	19	19	18	18	16	18	17	17	17	18	19	19	18	19
Olezarsen 80 mg	22	18	19	19	19	17	18	19	20	18	19	18	19	17	19	18	18	17	19	17	19	16	19	14	18	16	19

Abbreviations: SEM = standard error of the mean

Figure 12: Study CS3: Mean Platelet Counts and Platelet Count Changes Over Time (Safety Set)

No patient with a platelet count < LLN experienced a concurrent serious or severe clinical bleeding event. In general, patients with low platelet counts during the observation period tended to have platelet counts that were close to the LLN at Baseline.

The mean (SD) time to the first post-Baseline platelet count reduction to < 100,000/mm^3 was greater in the olezarsen 50 mg group (202.2 [123.28] days) compared with the olezarsen 80 mg group (37.4 [40.45] days) and the placebo group (70.0 [126.44] days).

Study drug was interrupted for 4 patients (all from olezarsen 80 mg group) due to low platelet counts. Two of these 4 patients experienced moderate platelet count reductions and the other 2 patients experienced mild platelet count reductions. The platelet counts improved to > 100,000/mm^3 in all 4 patients and no concurrent bleeding TEAEs were reported.

Abnormal post-Baseline platelet counts are summarized below.

Table 44: *Study CS3: Summary of Abnormal Post-Baseline Observed Platelet Count Results (Safety Set)*

Abnormality, n (%)	**Placebo (N = 23)**	**Olezarsen 50 mg (N = 21)**	**Olezarsen 80 mg (N = 22)**	**Total Olezarsen (N = 43)**
Any 2 occurrences of platelet count < 140,000/mm^3	6 (26.1)	10 (47.6)	13 (59.1)	23 (53.5)
Any single occurrence of platelet count < 100,000/mm^3	5 (21.7)	6 (28.6)	5 (22.7)	11 (25.6)
Any 2 occurrences of platelet count < 140,000/mm^3 on different days or any single occurrence of platelet count < 100,000/mm^3	7 (30.4)	11 (52.4)	13 (59.1)	24 (55.8)
≥ 140,000/mm^3	15 (65.2)	10 (47.6)	8 (36.4)	18 (41.9)
100,000/mm^3 to < 140,000/mm^3	3 (13.0)	5 (23.8)	9 (40.9)	14 (32.6)
75,000/mm^3 to < 100,000/mm^3	3 (13.0)	5 (23.8)	3 (13.6)	8 (18.6)
50,000/mm^3 to < 75,000/mm^3	1 (4.3)	1 (4.8)	2 (9.1)	3 (7.0)
25,000/mm^3 to < 50,000/mm^3	0	0	0	0
0 to < 25,000/mm^3	1 (4.3) [a]	0	0	0
≥ 30% decrease from Baseline	7 (30.4)	9 (42.9)	11 (50.0)	20 (46.5)
≥ 50% decrease from Baseline	3 (13.0)	2 (9.5)	2 (9.1)	4 (9.3)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: Patients with more than 1 value were counted once under the worst category.
Note: The Baseline for platelet was defined as the average of all assessments prior to the first dose of study drug.
Note: Both local and central laboratory results were used.
[a] Blood sample below 25,000/mm^3 (actual count 18,000/mm^3) was not analyzed by central lab until 24 days after collection. A local lab result on the same day was > 140,000/mm^3 (actual count 165,000/mm^3).

Shifts in toxicity grades from Baseline to worst post-Baseline value during the study for platelets decreased are summarized in the table below.

Table 45: Study CS3: Summary of Shift in CTCAE Grades from Baseline to Worst (Minimum) Post-Baseline Platelets Decreased (Safety Set)

Platelets decreased, n (%)		**Worst (Minimum) Post-Baseline**			
Treatment Group	**Baseline Grade**	> LLN	< LLN - 75,000/mm^3	< 75,000/mm^3 - 50,000/mm^3	< 50,000/mm^3
Olezarsen 80 mg	> LLN	8 (36.4)	11 (50.0)	1 (4.5)	0
	< LLN - 75,000/mm^3	0	1 (4.5)	1 (4.5)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Olezarsen 50 mg	> LLN	9 (42.9)	7 (33.3)	1 (4.8)	0
	< LLN - 75,000/mm^3	1 (4.8)	3 (14.3)	0	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Placebo	> LLN	15 (65.2)	3 (13.0)	0	1 (4.3)
	< LLN - 75,000/mm^3	0	3 (13.0)	1 (4.3)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0

Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100
Note: The Baseline for platelets was defined as the average of all assessments prior to the first dose of study drug. If a patient had a Baseline value but had no post-Baseline values, then the worst value was labeled as "unknown". Both local and

central laboratory data were used for platelet analysis. If a patient had a missing Baseline value but had a post-Baseline value, then the Baseline assessment was labeled as "unknown".

Note: Toxicity grades were based on CTCAE Version 5.0, November 2017: mild = < LLN - 75,000/mm^3; moderate = < 75,000 - 50,000/mm^3 to; severe = < 50,000 /mm^3.

Note: If normal range was missing then 140,000 /mm^3 was used as a LLN.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal

Pool 1 (CS3 + CS8)

Table 46: Thrombocytopenia TEAEs by Preferred Term (CS3, CS8, and Pool 1)

	Study CS3				**Study CS8**				**Pool 1 Study CS3 + Study CS8**			
		Olezarsen				**Olezarsen**				**Olezarsen**		
System Organ Class Preferred Term	**Placebo (N = 23)**	**50 mg (N = 21)**	**80 mg (N = 22)**	**Total Olezarsen (N = 43)**	**Placebo (N = 39)**	**50 mg (N = 58)**	**80 mg (N = 57)**	**Total Olezarsen (N = 115)**	**Placebo (N = 62)**	**50 mg (N = 79)**	**80 mg (N = 79)**	**Total Olezarsen (N = 158)**
Patients with At Least One Thrombocytopenia TEAE, n (%)	1 (4.3)	2 (9.5)	3 (13.6)	5 (11.6)	0	0	2 (3.5)	2 (1.7)	1 (1.3)	2 (2.9)	5 (6.6)	7 (4.8)
Investigations												
Platelet count decreased	1 (4.3)	1 (4.8)	3 (13.6)	4 (9.3)	0	0	1 (1.8)	1 (0.9)	1 (1.3)	1 (1.5)	4 (5.4)	5 (3.5)
Blood and lymphatic system disorders												
Thrombocytopenia	0	1 (4.8)	0	1 (2.3)	0	0	1 (1.8)	1 (0.9)	0	1 (1.5)	1 (1.2)	2 (1.3)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8).

Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100.

Note: A TEAE was defined as any AE starting or worsening on or after the first dose of the study drug.

Note: For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.

Note: Thrombocytopenia AEs was identified based on the 'Thrombocytopenia' High Level Terms or 'Platelet count decreased' preferred term using MedDRA Version 26.0.

Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.

None of the patients with thrombocytopenia TEAEs experienced concurrent clinical bleeding events, met the predefined stopping rule regarding platelet counts leading to study drug discontinuation, or permanently discontinued treatment due to a thrombocytopenia TEAE. Most thrombocytopenia TEAEs were mild in severity, and there were no severe thrombocytopenia TEAEs.

The mean (SD) time to onset of the first post-Baseline platelet count reduction to < 100,000/mm^3 was greater in the olezarsen 50 mg group (202.2 [123.28] days) compared with the olezarsen 80 mg group (69.4 [81.11] days) and the placebo group (110.0 [149.63] days).

Table 47: Summary of Abnormal Post-Baseline Platelet Count Results (Pool 1)

Abnormality, n (%)	Pool 1 Study CS3 + Study CS8			
		Olezarsen		
	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Any 2 occurrences of platelet count < 140,000/mm^3	7 (9.8)	13 (18.2)	19 (25.4)	32 (21.8)
Any single occurrence of platelet count < 100,000/mm^3	6 (8.4)	6 (8.8)	8 (10.6)	14 (9.7)
Any 2 occurrences of platelet count < 140,000/mm^3 on different days or any single occurrence of platelet count < 100,000/mm^3	8 (11.1)	14 (19.7)	19 (25.4)	33 (22.5)
Worst Post-Baseline Value				
100,000/mm^3 to < 140,000/mm^3	3 (4.0)	15 (19.3)	16 (21.1)	31 (20.2)
75,000/mm^3 to < 100,000/mm^3	3 (4.0)	5 (7.3)	6 (7.8)	11 (7.5)
50,000/mm^3 to < 75,000/mm^3	2 (3.1)	1 (1.5)	2 (2.8)	3 (2.1)
25,000/mm^3 to < 50,000/mm^3	0	0	0	0
0 to < 25,000/mm^3	1 (1.3) a	0	0	0
≥ 30% decrease from Baseline (single occurrence)	9 (12.9)	21 (27.5)	25 (32.4)	46 (29.9)
≥ 50% decrease from Baseline (single occurrence)	4 (5.8)	3 (4.1)	5 (6.4)	8 (5.3)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.
Note: Source table uses the units, platelets/mm^3, which is equivalent to platelets × 10^9/L.
Note: Baseline for platelets was defined as the average of all non-missing assessments prior to the first dose of study drug. Both local and central laboratory data were used for platelet analysis.
[a] Blood sample below 25,000/mm^3 (actual count 18,000/mm^3) was not analyzed by central lab until 24 days after collection. A local lab result on the same day was > 140,000/mm^3 (actual count 165,000/mm^3).
Abbreviations: CMH = Cochran-Mantel-Haenszel

Shift in toxicity grades from Baseline to minimum post-Baseline platelets decrease value are summarized in the table below.

Table 48: Summary of Shift in Toxicity Grades from Baseline to Minimum Post-Baseline Platelets Decrease Value (Pool 1)

Platelets decreased, n (%)		**Minimum Post-Baseline**			
Treatment Group	**Baseline Grade**	> LLN	< LLN - 75,000/mm^3	< 75,000/mm^3 - 50,000/mm^3	< 50,000/mm^3
Olezarsen 80 mg	> LLN	55 (68.3)	19 (25.1)	1 (1.4)	0
	< LLN - 75,000/mm^3	0	3 (3.8)	1 (1.4)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Olezarsen 50 mg	> LLN	57 (70.5)	17 (22.2)	1 (1.5)	0
	< LLN - 75,000/mm^3	1 (1.5)	3 (4.4)	0	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Placebo	> LLN	53 (87.5)	4 (5.3)	0	1 (1.3)
	< LLN - 75,000/mm^3	0	2 (2.7)	2 (3.1)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.
Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to receiving the first dose of olezarsen or placebo.
Platelet count Baseline was defined as the average of all pre-dose assessments prior to receiving the first dose of olezarsen or placebo. All scheduled and unscheduled, central, and local lab assessments were included. All scheduled and unscheduled, central and local lab assessments were included.
Note: Toxicity grades were based on CTCAE Version 5.0, November 2017: mild = < LLN - 75,000/mm^3; moderate = < 75,000/mm^3 - 50,000/mm^3; severe = < 50,000 /mm^3.
Note: If normal range was missing then 140,000 /mm^3 used as a LLN
Abbreviations: CMH = Cochran-Mantel-Haenszel; CTCAE = common terminology criteria for adverse events; LLN = lower limit of normal

Pool 4 (CS3 + CS13 + CS7)

The only OAEIs of thrombocytopenia TEAE in Pool 4 were derived from study CS3.

Table 49: Thrombocytopenia TEAEs by Preferred Term Safety Set – Pool 4

System Organ Class **Preferred Term**	**Placebo (N=23)** **n (%)**	**Olezarsen 50mg/80mg (N=21)** **n (%)**	**Olezarsen 80mg (N=66)** **n (%)**	**Total Olezarsen (N=87)** **n (%)**
Patients with any Thrombocytopenia TEAEs	***1 (4.3)***	***2 (9.5)***	***3 (4.5)***	***5 (5.7)***
Investigations	**1 (4.3)**	**1 (4.8)**	**3 (4.5)**	**4 (4.6)**
Platelet count decreased	1 (4.3)	1 (4.8)	3 (4.5)	4 (4.6)
Blood and lymphatic system disorders	**0**	**1 (4.8)**	**0**	**1 (1.1)**
Thrombocytopenia	0	1 (4.8)	0	1 (1.1)

The mean (SD) time to onset of the first post-Baseline platelet count reduction to < 100,000/mm^3 was greater in the olezarsen 50 mg/80 mg group (202.2 [123.28] days) compared with the olezarsen 80 mg group (71.1 [102.02] days) and the placebo group (70.0 [126.44] days).

Table 50: Summary of Abnormal Post-Baseline Platelet Count Results (Pool 4)

Abnormality, n (%)	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	Olezarsen 50 mg/80 mg (N = 21)	Olezarsen 80 mg (N = 66)	Total Olezarsen (N = 87)
Any 2 occurrences of platelet count < 140,000/mm^3	6 (26.1)	11 (52.4)	34 (51.5)	45 (51.7)
Any single occurrence of platelet count < 100,000/mm^3	5 (21.7)	6 (28.6)	14 (21.2)	20 (23.0)
Any 2 occurrences of platelet count < 140,000/mm^3 on different days or any single occurrence of platelet count < 100,000/mm^3	7 (30.4)	11 (52.4)	34 (51.5)	45 (51.7)
Worst Post-Baseline Value				
100,000/mm^3 to < 140,000/mm^3	3 (13.0)	5 (23.8)	25 (37.9)	30 (34.5)
75,000/mm^3 to < 100,000/mm^3	3 (13.0)	5 (23.8)	10 (15.2)	15 (17.2)
50,000/mm^3 to < 75,000/mm^3	1 (4.3)	1 (4.8)	4 (6.1)	5 (5.7)
25,000/mm^3 to < 50,000/mm^3	0	0	0	0
0 to < 25,000/mm^3	1 (4.3) a	0	0	0
≥ 30% decrease from Baseline (single occurrence)	7 (30.4)	10 (47.6)	35 (53.0)	45 (51.7)
≥ 50% decrease from Baseline (single occurrence)	3 (13.0)	2 (9.5)	8 (12.1)	10 (11.5)

Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100.

Note: Platelet count and worst platelet % change from Baseline were presented for patients with normal Baseline platelet counts. Platelet count Baseline was defined as the average of all pre-dose assessments prior to receiving the first dose of olezarsen or placebo. All scheduled and unscheduled, central, and local lab assessments were included. For patients who received olezarsen in CS3 (index study) and rolled over to CS13, the index study Baseline was used as the CS13 Baseline. For patients who received placebo in CS3 and rolled over to CS13, CS13 Baseline was defined as the average of all assessments within 31 days prior to the first dose of olezarsen in CS13.

Note: All scheduled and unscheduled, central, and local lab assessments were included.

Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.

Note: Source table uses the units, platelets/mm^3, which is equivalent to platelets × 10^9/L.

[a] Blood sample below 25,000/mm^3 (actual count 18,000/mm^3) was not analyzed by central lab until 24 days after collection. A local lab result on the same day was > 140,000/mm^3 (actual count 165,000/mm^3).

No patients across all treatment groups had a Baseline severity grade of moderate or severe, and most patients with a Baseline severity grade of mild remained mild throughout the study.

Table 51: Summary of Shift in Toxicity Grades from Baseline to Minimum Post-Baseline Platelets Decrease Value (Pool 4)

Platelets decreased, n (%)		**Minimum Post-Baseline**			
Treatment Group	**Baseline Grade**	> LLN	< LLN - 75,000/mm^3	< 75,000/mm^3 - 50,000/mm^3	< 50,000/mm^3
Olezarsen 80 mg	> LLN	27 (40.9)	27 (40.9)	1 (1.5)	0
	< LLN - 75,000/mm^3	0	8 (12.1)	3 (4.5)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Olezarsen 50 mg/80 mg	> LLN	9 (42.9)	7 (33.3)	1 (4.8)	0
	< LLN - 75,000/mm^3	1 (4.8)	3 (14.3)	0	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Placebo	> LLN	15 (65.2)	4 (17.4)	0	1 (4.3)
	< LLN - 75,000/mm^3	0	2 (8.7)	1 (4.3)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0

Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: If a patient had a Baseline value but had no post-Baseline values, then the minimum value was labeled as 'Unknown'. If a patient had a missing Baseline value but had a post-Baseline value, then the Baseline assessment was labeled as 'Unknown'.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The olezarsen 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to olezarsen 80 mg and then had their dose reduced to 50 mg.
Note: Platelet count Baseline was defined as the average of all pre-dose assessments prior to receiving the first dose of olezarsen or placebo. All scheduled and unscheduled, central, and local lab assessments were included. For patients who received olezarsen in CS3 (index study) and rolled over to CS13, the index study Baseline was used as the Baseline. For patients who received placebo in CS3 and rolled over to CS13, platelet count Baseline was defined as the average of all assessments within 31 days prior to the first dose of olezarsen in CS13. All scheduled and unscheduled, central, and local lab assessments were included.
Note: Toxicity grades were based on the CTCAE Version 5.0, November 2017. mild = 75,000 cell/mm^3 to < LLN; moderate = < 75,000 to 50,000 cell/mm^3; severe = < 50,000 cell/mm^3.
Note: If normal range was missing then 140,000 cell/mm^3 used as a LLN.
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Table 52: Thrombocytopenia TEAEs by Preferred Term Safety Set – Pool 5

System Organ Class **Preferred Term**	**Placebo (N=86)** **n (%)**	**Olezarsen 10-40mg (N=68)** **n (%)**	**Olezarsen 50mg/80mg (N=101)** **n (%)**	**Olezarsen 80mg (N=123)** **n (%)**	**Total Olezarsen (N=292)** **n (%)**
Patients with any Thrombocytopenia TEAEs	1 (1.2)	1 (1.5)	2 (2.0)	5 (4.1)	8 (2.7)
Investigations	1 (1.2)	0	1 (1.0)	4 (3.3)	5 (1.7)
Platelet count decreased	1 (1.2)	0	1 (1.0)	4 (3.3)	5 (1.7)
Blood and lymphatic system disorders	0	1 (1.5)	1 (1.0)	1 (0.8)	3 (1.0)
Thrombocytopenia	0	1 (1.5)	1 (1.0)	1 (0.8)	3 (1.0)

No patient in any treatment group met the predefined stopping rule regarding platelet counts leading to study drug discontinuation, or discontinued treatment due to a thrombocytopenia TEAE, and no

patients with platelet count < LLN experienced concurrent serious or severe clinical bleeding event. Most thrombocytopenia TEAEs were mild in severity, and there were no severe thrombocytopenia TEAEs.

In addition to the one patient on placebo in Study CS3 who experienced a platelet count reduction below 25,000/mm^3, there were two instances of platelet counts < 100,000/mm^3, likely attributable to laboratory errors, for two patients in Study CS2.

The mean (SD) time to onset of the first post-Baseline platelet count reduction to < 100,000/mm^3 was greater in the olezarsen 50 mg/80 mg group (202.2 [123.28] days) compared with the olezarsen 80 mg group (80.2 [102.39] days), the olezarsen 10-40 mg group (128.0 days) and the placebo group (118.4 [138.40] days).

Table 53: Summary of Abnormal Post-Baseline Platelet Count Results (Pool 5)

	Pool 5 Study CS2 + Study CS3 + Study CS7 + Study CS8 + Study CS13				
		Olezarsen			
Abnormality, n (%)	**Placebo (N = 86)**	**10-40 mg (N = 68)**	**50 mg/80 mg (N = 101)**	**80 mg (N = 123)**	**Total Olezarsen (N = 292)**
Any 2 occurrences of platelet count < 140,000/mm^3	8 (9.3)	6 (8.8)	16 (15.8)	40 (32.5)	62 (21.2)
Any single occurrence of platelet count < 100,000/mm^3	7 (8.1)	1 (1.5)	6 (5.9)	17 (13.8)	24 (8.2)
Any 2 occurrences of platelet count < 140,000/mm^3 on different days or any single occurrence of platelet count < 100,000/mm^3	9 (10.5)	6 (8.8)	16 (15.8)	40 (32.5)	62 (21.2)
Worst Post-Baseline value					
100,000/mm^3 to < 140,000/mm^3	5 (5.8)	8 (11.8)	18 (17.8)	32 (26.0)	58 (19.9)
75,000/mm^3 to < 100,000/mm^3	3 (3.5)	0	5 (5.0)	13 (10.6)	18 (6.2)
50,000/mm^3 to < 75,000/mm^3	2 (2.3)	1 (1.5)	1 (1.0)	4 (3.3)	6 (2.1)
25,000/mm^3 to < 50,000/mm^3	1 (1.2)	0	0	0	0
0 to < 25,000/mm^3	1 (1.2)	0	0	0	0
≥ 30% decrease from Baseline (single occurrence)	11 (12.8)	6 (8.8)	24 (23.8)	49 (39.8)	79 (27.1)
≥ 50% decrease from Baseline (single occurrence)	5 (5.8)	2 (2.9)	3 (3.0)	11 (8.9)	16 (5.5)

Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100.

No patients across all treatment groups had a Baseline severity grade of moderate or severe for platelet counts, and most patients with a Baseline severity grade of mild remained mild throughout the study.

Table 54: Summary of Shift in Toxicity Grades from Baseline to Minimum Post-Baseline Platelets Decrease Value (Pool 5)

Platelets decreased, n (%)		Minimum Post-Baseline			
Treatment Group	Baseline Grade	> LLN	< LLN - 75,000/mm^3	< 75,000/mm^3 - 50,000/mm^3	< 50,000/mm^3
Olezarsen 80 mg	> LLN	74 (60.2)	35 (28.5)	1 (0.8)	0
	< LLN - 75,000/mm^3	0	10 (8.1)	3 (2.4)	0
	< 75,000/mm^3 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Olezarsen 50 mg/80 mg	> LLN	75 (74.3)	20 (19.8)	1 (1.0)	0
	< LLN - 75,000/mm^3	1 (1.0)	4 (4.0)	0	0
	< 75,000 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Olezarsen 10-40 mg	> LLN	56 (82.4)	10 (14.7)	1 (1.5)	0
	< LLN - 75,000/mm^3	1 (1.5)	0	0	0
	< 75,000 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0
Placebo	> LLN	73 (84.9)	7 (8.1)	0	2 (2.3)
	< LLN - 75,000/mm^3	0	2 (2.3)	2 (2.3)	0
	< 75,000 - 50,000/mm^3	0	0	0	0
	< 50,000/mm^3	0	0	0	0

Note: The olezarsen 50 mg/80 mg group includes:
- Patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13.
- Patients who were randomized to and received olezarsen 50 mg Q4W in CS2.
- Patients who were randomized to and received olezarsen 50 mg in CS8.
- Patients who were initially randomized to olezarsen 80 mg in CS3 or CS8 and then had their dose reduced to 50 mg are not being included in this group.

Hypersensitivity Adverse Events

Pool 1 (CS3 + CS8)

All OAEIs of hypersensitivity were non-serious, and mild or moderate in severity; no hypersensitivity OAEI required dose reduction, but 3 hypersensitivity OAEIs led to permanent study drug discontinuation: flushing (2 patients in the olezarsen 80 mg group) and injection site urticaria (1 patient in the olezarsen 50 mg group).

The mean (SD) time to onset of the first post-Baseline hypersensitivity reactions was greater in the placebo group (170.0 days) compared with the olezarsen 80 mg group (17.7 [28.87] days) and the olezarsen 50 mg group (115.1 [49.81] days).

Table 55: Hypersensitivity by FMQ (Narrow), FMQ (Broad), Algorithmic FMQ, and Anaphylactic Reaction FMQ (Narrow) by Preferred Term (CS3, CS8, and Pool 1)

	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with At Least One TEAE by Hypersensitivity FMQ (Narrow), n (%)	0	0	0	0	0	0	0	0	0	0	0	0

	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with at least one TEAE by Hypersensitivity FMQ (Broad), n (%)	1 (4.3)	2 (9.5)	2 (9.1)	4 (9.3)	0	5 (8.6)	1 (1.8)	6 (5.2)	1 (1.3)	7 (8.9)	3 (4.0)	10 (6.5)
Asthma	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Blood pressure decreased	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Flushing	0	1 (4.8)	1 (4.5)	2 (4.7)	0	0	1 (1.8)	1 (0.9)	0	1 (1.5)	2 (2.6)	3 (2.0)
Injection site urticaria	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Pruritis	0	1 (4.8)	0	1 (2.3)	0	1 (1.7)	0	1 (0.9)	0	2 (2.7)	0	2 (1.3)
Rash	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Rash macular	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Swelling	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Patients with at least one TEAE by Hypersensitivity Algorithmic FMQ, n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Patients with at least one TEAE by Anaphylactic Reaction FMQ (Narrow), n (%)	0	0	0	0	0	0	0	0	0	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: A TEAE was defined as any AE starting or worsening on or after the first dose of the study drug.
Note: For the summarization of number of patients (n), a patient was counted only once for each System Organ Class and Preferred Term even if > 1 event was reported.
Note: Hypersensitivity AEs was identified based on export from MedDRA Version 26.0.
Note: Pooled proportions are adjusted by study using CMH approach. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; FMQ = FDA MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event

Pool 4 (CS3 + CS13 + CS7)

OAEIs of hypersensitivity were generally non-serious and mild or moderate in severity; no OAEI required dose reduction, but 4 OAEIs lead to permanent study drug discontinuation: flushing (1 patient in the olezarsen 80 mg group), hypersensitivity (1 patient in the olezarsen 80 mg group), anaphylactic reaction (1 patient in the CS3-olezarsen 80 mg group), and hypersensitivity (1 patient in the CS3-placebo group).

The mean (SD) time to onset of the first post-Baseline hypersensitivity reactions was greater in the olezarsen 50 mg/80 mg group (252.3 [311.87] days) compared with the olezarsen 80 mg group (191.4 [242.23] days) and the placebo group (170.0 days).

Table 56: Hypersensitivity by FMQ (Narrow), FMQ (Broad), Algorithmic FMQ, and Anaphylactic Reaction FMQ (Narrow) by Preferred Term (Pool 4)

	Pool 4 **Study CS3 + Study CS7 + Study CS13**			
		Olezarsen		
	Placebo **(N = 23)**	**50 mg/80 mg** **(N = 21)**	**80 mg** **(N = 66)**	**Total Olezarsen** **(N = 87)**
Patients with at least one TEAE by Hypersensitivity FMQ (Narrow), n (%)	0	0	3 (4.5)	3 (4.5)
Anaphylactic reaction	0	0	1 (1.5)	1 (1.1)
Hypersensitivity	0	0	2 (3.0)	2 (2.3)
Patients with at least one TEAE by Hypersensitivity FMQ (Broad), n (%)	1 (4.3)	3 (14.3)	9 (13.6)	12 (13.8)
Anaphylactic reaction	0	0	1 (1.5)	1 (1.1)
Flushing	0	1 (4.8)	1 (1.5)	2 (2.3)
Gingival swelling	0	1 (4.8)	0	1 (1.1)
Hypersensitivity	0	0	2 (3.0)	2 (2.3)
Injection related reaction	0	1 (4.8)	0	1 (1.1)
Injection site urticaria	0	0	2 (3.0)	2 (2.3)
Pruritus	0	1 (4.8)	0	1 (1.1)
Rash	0	0	1 (1.5)	1 (1.1)
Rash erythematous	0	0	1 (1.5)	1 (1.1)
Rash macular	1 (4.3)	0	0	0
Swelling	0	0	1 (1.5)	1 (1.1)
Patients with at least one TEAE by Hypersensitivity Algorithmic FMQ, n (%)	0	0	3 (4.5)	3 (3.4)
Category A (Non-algorithmic narrow FMQ)	0	0	3 (4.5)	3 (3.4)
Patients with at least one TEAE by Anaphylactic Reaction FMQ (Narrow), n (%)	0	0	1 (1.5)	1 (1.1)
Anaphylactic reaction	0	0	1 (1.5)	1 (1.1)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

OAEIs of hypersensitivity were in general non-serious, and mild or moderate in severity (except 1 serious severe event of Henoch Schonlein purpura in the placebo group, 1 serious moderate event of hypersensitivity in the olezarsen 80 mg group, 1 serious severe event of anaphylactic reaction in the CS3-olezarsen 80 mg group, and 1 serious severe event of hypersensitivity in the CS3-placebo group); no OAEI required dose reduction, but 7 OAEIs led to permanent study drug discontinuation.

Table 57: Hypersensitivity by FMQ (Narrow), FMQ (Broad), Algorithmic FMQ, and Anaphylactic Reaction FMQ (Narrow) by Preferred Term (Pool 5)

	Pool 5 **Study CS2 + Study CS3 + Study CS7 + Study CS8 + Study CS13**				
		Olezarsen			
	Placebo (N = 86)	**10-40 mg (N = 68)**	**50 mg/80 mg (N = 101)**	**80 mg (N = 123)**	**Total Olezarsen (N = 292)**
Patients with at least one TEAE by Hypersensitivity FMQ (Narrow), n (%)	0	0	1 (1.0)	3 (2.4)	4 (1.4)
Anaphylactic reaction	0	0	0	1 (0.8)	1 (0.3)
Hypersensitivity	0	0	1 (1.0)	2 (1.6)	3 (1.0)
Patients with at least one TEAE by Hypersensitivity FMQ (Broad), n (%)	5 (5.8)	11 (16.2)	14 (13.9)	10 (8.1)	35 (12.0)
Anaphylactic reaction	0	0	0	1 (0.8)	1 (0.3)
Asthma	0	0	1 (1.0)	0	1 (0.3)
Blood pressure decreased	0	0	1 (1.0)	0	1 (0.3)
Eosinophil count increased	0	1 (1.5)	0	0	1 (0.3)
Eosinophilia	1 (1.2)	0	0	0	0
Erythema	0	3 (4.4)	2 (2.0)	0	5 (1.7)
Flushing	0	1 (1.5)	1 (1.0)	2 (1.6)	4 (1.4)
Gingival swelling	0	0	1 (1.0)	0	1 (0.3)
Henoch-Schonlein purpura	1 (1.2)	0	0	0	0
Hypersensitivity	0	0	1 (1.0)	2 (1.6)	3 (1.0)
Injection related reaction	0	0	1 (1.0)	0	1 (0.3)
Injection site rash	0	2 (2.9)	1 (1.0)	0	3 (1.0)
Injection site urticaria	0	1 (1.5)	1 (1.0)	2 (1.6)	4 (1.4)
Pruritus	1 (1.2)	1 (1.5)	4 (4.0)	0	5 (1.7)
Rash	0	3 (4.4)	2 (2.0)	1 (0.8)	6 (2.1)
Rash erythematous	0	0	0	1 (0.8)	1 (0.3)
Rash macular	1 (1.2)	0	0	0	0
Rash maculo-papular	1 (1.2)	0	0	0	0
Rash vesicular	1 (1.2)	1 (1.5)	0	0	1 (0.3)
Skin exfoliation	0	1 (1.5)	0	0	1 (0.3)
Swelling	0	0	0	1 (0.8)	1 (0.3)
Wheezing	0	1 (1.5)	0	0	1 (0.3)
Patients with at least one TEAE by Hypersensitivity Algorithmic FMQ, n (%)	0	0	1 (1.0)	3 (2.4)	4 (1.4)
Category A (Non-algorithmic narrow FMQ)	0	0	1 (1.0)	3 (2.4)	4 (1.4)
Patients with at least one TEAE by Anaphylactic Reaction FMQ (Narrow), n (%)	0	0	0	1 (0.8)	1 (0.3)
Anaphylactic reaction	0	0	0	1 (0.8)	1 (0.3)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.

Renal Impairment Adverse Events

Study CS3

No patients in the olezarsen 80 mg or 50 mg groups experienced a TEAE meeting the criteria for the Acute Renal Failure SMQ (narrow or broad), compared with 2 (8.7%) patients in the placebo group who experienced TEAEs of proteinuria. No patient met the criteria for Acute Kidney Injury FMQ (narrow or broad). No patient died, experienced a serious TEAE, was permanently discontinued from study drug, or required a dose modification due to renal impairment OAEI.

Potential cases of renal impairment were also examined by evaluation of laboratory parameters.

Serum Creatinine: Mean percent change from Baseline in serum creatinine over time was variable for all treatment groups, and there was no clear pattern for a dose-related effect from olezarsen

eGFR: The mean (SD) time to onset of the first post-Baseline eGFR ≥25% decrease from Baseline was greater in the olezarsen 50 mg group (194.0 [250.32] days) compared with the olezarsen 80 mg group (72.0 [1.41] days), and the placebo group (93.4 [25.93] days), respectively.

UACR: Mean percent changes from Baseline in UACR over time were similar for all groups, except for a single time point, Week 33, when there was a notable increase in the mean percent change from Baseline in the placebo group. This was driven by a single patient that had increases in UACR.

The mean (SD) time to onset of the first post-Baseline TEAE of albuminuria was greater in the olezarsen 80 mg group (310.0 days) compared with placebo group (267.5 [60.10] days). No patient in the olezarsen 50 mg group had a TEAE of albuminuria.

UPCR: Mean percent changes from Baseline in UPCR over time were similar for all groups, except for a single time point, Week 33, when there was a notable increase in the mean percent change from Baseline in the placebo group. This was driven by a single patient that had increases in UPCR.

The mean (SD) time to onset of the first post-Baseline TEAE of proteinuria was greater in the placebo group (267.5 [60.10] days) compared with olezarsen 80 mg group (100.0 days). No patient in the olezarsen 50 mg group had a TEAE of proteinuria.

Table 58: Study CS3: Summary of Abnormal Post-Baseline Renal Function Parameters (Safety Set)

Renal Function Parameter Abnormality Any time after first dose, n (%)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)	Total Olezarsen (N = 43)
Serum creatinine ≥ 2 × Baseline	1 (4.3)	1 (4.8)	0	1 (2.3)
Serum creatinine ≥ 3 × Baseline	0	1 (4.8)	0	1 (2.3)
eGFR ≥ 25% reduction from Baseline	5 (21.7)	2 (9.5)	2 (9.1)	4 (9.3)
eGFR ≥ 30% reduction from Baseline	4 (17.4)	2 (9.5)	2 (9.1)	4 (9.3)
eGFR ≥ 50% reduction from Baseline	1 (4.3)	0	0	0
eGFR ≥ 75% reduction from Baseline	0	0	0	0
UACR ≥ 300 mg/g	1 (4.3)	0	2 (9.1)	2 (4.7)
UACR ≥ 500 mg/g	1 (4.3)	0	0	0
UACR ≥ 600 mg/g	1 (4.3)	0	0	0
UACR ≥ 1200 mg/g	1 (4.3)	0	0	0
UACR ≥ 50% increase from Baseline	13 (56.5)	10 (47.6)	9 (40.9)	19 (44.2)
UPCR ≥ 500 mg/g	3 (13.0)	0	2 (9.1)	2 (4.7)
UPCR ≥ 1000 mg/g	2 (8.7)	0	0	0

Renal Function Parameter Abnormality Any time after first dose, n (%)	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)	Total Olezarsen (N = 43)
UPCR ≥ 2000 mg/g	0	0	0	0

Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: Baseline was defined as the last non-missing assessment prior to the first dose of study drug.
Abbreviations: eGFR = estimated glomerular filtration rate; UACR = urine albumin/creatinine ratio; UPCR = urine protein/creatinine ratio

Pool 1 (CS3 + CS8)

The mean (SD) time to onset of the first post-Baseline acute kidney injury FMQ (broad) was greater in the olezarsen 50 mg group (196.0 days) compared with the olezarsen 80 mg group (113.0 days) and the placebo group (103.7 [85.54] days).

Potential cases of renal impairment were also examined by evaluation of laboratory parameters.

Table 59: Summary of Post-Baseline Renal Function Parameter Results (Pool 1)

Renal Parameter Abnormality, n (%)	Pool 1 Study CS3 + Study CS8			
		Olezarsen		
	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Serum creatinine ≥ 0.3 mg/dL higher than Baseline	17 (26.7)	9 (11.3)	14 (17.7)	23 (14.5)
Serum creatinine ≥ 1.5 × Baseline	8 (11.6)	5 (6.8)	8 (10.4)	13 (8.6)
Serum creatinine ≥ 2.0 × Baseline	1 (1.3)	1 (1.5)	0	1 (0.7)
Serum creatinine ≥ 3.0 × Baseline	0	1 (1.5)	0	1 (0.7)
eGFR decrease from Baseline ≥ 25%	18 (29.8)	13 (16.1)	13 (16.2)	26 (16.1)
eGFR decrease from Baseline ≥ 30%	12 (19.6)	9 (11.3)	7 (8.9)	16 (10.1)
eGFR decrease from Baseline ≥ 50%	1 (1.3)	0	0	0
eGFR decrease from Baseline ≥ 75%	0	0	0	0
UACR ≥ 300 mg/g	6 (10.2)	6 (7.2)	5 (6.4)	11 (6.9)
UACR ≥ 500 mg/g	4 (6.7)	4 (4.8)	1 (1.2)	5 (3.0)
UACR ≥ 600 mg/g	4 (6.7)	2 (2.4)	1 (1.2)	3 (1.8)
UACR ≥ 1200 mg/g	2 (3.1)	1 (1.2)	1 (1.2)	2 (1.2)
UACR increase from Baseline ≥ 50%	13 (17.3)	10 (14.6)	9 (12.5)	19 (13.6)
UPCR ≥ 500 mg/g	14 (23.6)	8 (9.6)	11 (13.7)	19 (11.7)
UPCR ≥ 1000 mg/g	6 (9.8)	4 (4.8)	4 (4.9)	8 (4.8)
UPCR ≥ 2000 mg/g	1 (1.8)	1 (1.2)	1 (1.2)	2 (1.2)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.
Note: Baseline for other parameters is defined as the last non-missing assessment prior to the first dose of study drug.
Abbreviations: CMH = Cochran-Mantel-Haenszel; eGFR = estimated glomerular filtration rate; UACR = urine albumin/creatinine ratio; UPCR = urine protein/creatinine ratio

To be noted, that the population from the study CS3 study (FCS patients) had a lower proportion of patients with abnormal post-Baseline renal parameter results compared with the population from the study CS8 (hypertriglyceridemia patients), which was expected, as 14.3% of patients in the study CS8 had a medical history of chronic kidney disease.

Table 60: Renal Impairment Treatment-Emergent Adverse Events by Acute Renal Failure SMQ (Broad and Narrow) and System Organ Class and Preferred Term (CS3, CS8, and Pool 1)

System Organ Class/ Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with At Least One Renal Impairment TEAE, n (%)	2 (8.7)	0	0	0	5 (12.8)	2 (3.4)	1 (1.8)	3 (2.6)	7 (11.6)	2 (2.4)	1 (1.2)	3 (1.8)
Investigations												
Blood creatinine increased	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Glomerular filtration rate decreased	0	0	0	0	3 (7.7)	1 (1.7)	0	1 (0.9)	3 (5.3)	1 (No 1.2)	0	1 (0.6)
Renal and urinary disorders												
Proteinuria	2 (8.7)	0	0	0	1 (2.6)	1 (1.7)	0	1 (0.9)	3 (4.4)	1 (1.2)	0	1 (0.6)
Albuminuria	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8).
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: A TEAE was defined as any AE starting or worsening on or after the first dose of the study drug.
Note: For the summarization of number of patients (n), a patient was counted only once for each preferred term even if > 1 event was reported.
Note: Renal impairment AEs were identified based on the Acute Renal Failure SMQ (Narrow and Broad) Export from MedDRA Version 26.0.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event

Pool 4 (CS3 + CS13 + CS7)

Across all FCS population trials, a greater proportion of patients in the placebo group (8.7%) experienced renal impairment OAEIs that met the criteria for Acute Renal Failure SMQ (broad and narrow) compared with the olezarsen 80 mg group (4.5%); no patients in the olezarsen 50 mg/80 mg group experienced any renal impairment OAEIs. No patient died, experienced a serious renal impairment OAEI, or was permanently discontinued from study drug due to renal impairment OAEIs.

No patient met the criteria for Acute Kidney Injury FMQ (narrow). Two (3.0%) patients in the olezarsen 80 mg group experienced TEAEs that met the criteria for Acute Kidney Injury FMQ (broad); no patient in the olezarsen 50 mg/80 mg and the placebo groups had acute kidney injury FMQ (broad). The mean (SD) time to onset of the first post-Baseline acute kidney injury FMQ (broad) in the olezarsen 80 mg group was 199.5 (36.06) days.

eGFR: The mean (SD) time to onset of the first post-Baseline eGFR ≥25% decrease from Baseline was greater in the olezarsen 50 mg/80 mg group (331.0 [186.46] days) and the olezarsen 80 mg group (258.9 [238.95] days) compared with the placebo group (93.4 [25.93] days.

UACR: The mean (SD) time to onset of the first post-Baseline TEAE of albuminuria was greater in the olezarsen 80 mg group (310.0 days) compared with the placebo group (267.5 [60.10] days); no patient in the olezarsen 50 mg/80 mg group had TEAE of albuminuria.

UPCR: The mean (SD) time to onset of the first post-Baseline TEAE of proteinuria was greater in the olezarsen 50 mg/80 mg group (633.0 days) compared with the olezarsen 80 mg group (102.5 [47.75] days) and the placebo group (267.5 [60.10] days).

Table 61: Summary of Post-Baseline Renal Function Parameter Results (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
Renal Parameter Abnormality, n (%)	**Placebo (N = 23)**	**50 mg/80 mg (N = 21)**	**80 mg (N = 66)**	**Total Olezarsen (N = 87)**
Serum creatinine ≥ 0.3 mg/dL higher than Baseline	8 (34.8)	4 (19.0)	12 (18.2)	16 (18.4)
Serum creatinine ≥ 1.5 × Baseline	6 (26.1)	3 (14.3)	5 (7.6)	8 (9.2)
Serum creatinine ≥ 2.0 × Baseline	1 (4.3)	1 (4.8)	1 (1.5)	2 (2.3)
Serum creatinine ≥ 3.0 × Baseline	0	1 (4.8)	0	1 (1.1)
eGFR decrease from Baseline ≥ 25%	5 (21.7)	5 (23.8)	9 (13.6)	14 (16.1)
eGFR decrease from Baseline ≥ 30%	4 (17.4)	2 (9.5)	7 (10.6)	9 (10.3)
eGFR decrease from Baseline ≥ 50%	1 (4.3)	0	0	0
eGFR decrease from Baseline ≥ 75%	0	0	0	0
UACR ≥ 300 mg/g	1 (4.3)	2 (9.5)	8 (12.1)	10 (11.5)
UACR ≥ 500 mg/g	1 (4.3)	1 (4.8)	4 (6.1)	5 (5.7)
UACR ≥ 600 mg/g	1 (4.3)	1 (4.8)	4 (6.1)	5 (5.7)
UACR ≥ 1200 mg/g	1 (4.3)	0	3 (4.5)	3 (3.4)
UACR increase from Baseline ≥ 50%	13 (56.5)	11 (52.4)	39 (59.1)	50 (57.5)
UPCR ≥ 500 mg/g	3 (13.0)	2 (9.5)	9 (13.6)	11 (12.6)
UPCR ≥ 1000 mg/g	2 (8.7)	1 (4.8)	5 (7.6)	6 (6.9)
UPCR ≥ 2000 mg/g	0	0	2 (3.0)	2 (2.3)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: Patients who took placebo in CS3 then took olezarsen in CS13 were included in both placebo and active treatment groups.
Note: Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to receiving the first dose of olezarsen or placebo. For patients who received olezarsen in CS3 (Index Study) and rolled

over to CS13, the Index Study Baseline was used as the CS13 Baseline. For patients who received placebo in CS3 and rolled over to CS13, CS13 Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to the first dose of olezarsen in CS13.

Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.

Abbreviations: eGFR = estimated glomerular filtration rate; FCS = familial chylomicronemia syndrome; INR = international normalized ratio; UACR = urine albumin/creatinine ratio; ULN = upper limit of normal; UPCR = urine protein/creatinine ratio

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Across all olezarsen clinical trials, a greater proportion of patients in the placebo group (12.8%) experienced renal impairment OAEIs that met the criteria for Acute Renal Failure SMQ (broad and narrow) compared with the olezarsen 80 mg group (3.3%), the olezarsen 50 mg/80 mg group (3.0%), and the olezarsen 10-40 mg group (10.3%). No patient died, experienced a serious renal impairment OAEI, or was permanently discontinued from study drug due to renal impairment OAEIs.

No patient met the criteria for Acute Kidney Injury FMQ (narrow). A greater proportion of patients in the placebo group (8.1%) compared with the olezarsen 80 mg group (2.4%), the olezarsen 50 mg/80 mg group (2.0%), and olezarsen 10-40 mg group (7.4%) experienced TEAEs that met the criteria for Acute Kidney Injury FMQ (broad).

Table 62: Summary of Post-Baseline Renal Function Parameter Results (Pool 5)

	Pool 5 Study CS2 + Study CS3 + Study CS7 + Study CS8 + Study CS13				
		Olezarsen			
Renal Parameter Abnormality, n (%)	**Placebo (N = 86)**	**10-40 mg (N = 68)**	**50 mg/80 mg (N = 101)**	**80 mg (N = 123)**	**Total Olezarsen (N = 292)**
Serum creatinine ≥ 0.3 mg/dL higher than Baseline	21 (24.4)	15 (22.1)	11 (10.9)	22 (17.9)	48 (16.4)
Serum creatinine ≥ 1.5 × Baseline	9 (10.5)	5 (7.4)	5 (5.0)	9 (7.3)	19 (6.5)
Serum creatinine ≥ 2.0 × Baseline	1 (1.2)	1 (1.5)	1 (1.0)	1 (0.8)	3 (1.0)
Serum creatinine ≥ 3.0 × Baseline	0	0	1 (1.0)	0	1 (0.3)
eGFR decrease from Baseline ≥ 25%	24 (27.9)	18 (26.5)	20 (19.8)	20 (16.3)	58 (19.9)
eGFR decrease from Baseline ≥ 30%	15 (17.4)	9 (13.2)	10 (9.9)	12 (9.8)	31 (10.6)
eGFR decrease from Baseline ≥ 50%	1 (1.2)	1 (1.5)	0	0	1 (0.3)
eGFR decrease from Baseline ≥ 75%	0	0	0	0	0
UACR ≥ 300 mg/g	6 (7.0)	3 (4.4)	9 (8.9)	11 (8.9)	23 (7.9)
UACR ≥ 500 mg/g	4 (4.7)	1 (1.5)	5 (5.0)	5 (4.1)	11 (3.8)
UACR ≥ 600 mg/g	4 (4.7)	1 (1.5)	3 (3.0)	5 (4.1)	9 (3.1)
UACR ≥ 1200 mg/g	2 (2.3)	0	1 (1.0)	4 (3.3)	5 (1.7)
UACR increase from Baseline ≥ 50%	33 (38.4)	43 (63.2)	26 (25.7)	39 (31.7)	108 (37.0)
UPCR ≥ 500 mg/g	14 (16.3)	4 (5.9)	10 (9.9)	18 (14.6)	32 (11.0)
UPCR ≥ 1000 mg/g	6 (7.0)	2 (2.9)	5 (5.0)	9 (7.3)	16 (5.5)
UPCR ≥ 2000 mg/g	1 (1.2)	0	1 (1.0)	3 (2.4)	4 (1.4)

Pool 5: All population studies (CS3 + CS13 + CS7 + CS2 + CS8)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.

Note: Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to receiving the first dose of olezarsen or placebo. For patients who received olezarsen in CS3 (Index Study) and rolled over to CS13, the Index Study Baseline was used as the CS13 Baseline. For patients who received placebo in CS3 and rolled over to CS13, CS13 Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to the first dose of olezarsen in CS13.

Note: For patients who received olezarsen in CS3 (Index Study) and rolled over to CS13, the Index Study Baseline was used as the CS13 Baseline. For patients who received placebo in CS3 and rolled over to CS13, CS13 Baseline was defined as the average of all assessments within 31 days prior to the first dose of olezarsen in CS13.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: All scheduled and unscheduled, central, and local lab assessments were included.
Abbreviations: eGFR = estimated glomerular filtration rate; UACR = urine albumin/creatinine ratio; UPCR = urine protein/creatinine ratio

Abnormal Liver Function Adverse events

Study CS3

Table 63: Study CS3: Summary of Treatment-emergent Abnormal Liver Function OAEI by Hepatic Injury FMQ (Narrow) by Preferred Term (Safety Set)

	Placebo (N = 23)	Olezarsen 50 mg (N = 21)	Olezarsen 80 mg (N = 22)	Total Olezarsen (N = 43)
Patients with at least one Treatment-emergent Adverse Events by Hepatic Injury FMQ (Narrow), n (%)	**2 (8.7)**	**0**	**2 (9.1)**	**2 (4.7)**
Alanine aminotransferase increased	1 (4.3)	0	1 (4.5)	1 (2.3)
Aspartate aminotransferase increased	1 (4.3)	0	1 (4.5)	1 (2.3)
Gastric varices	1 (4.3)	0	0	0
Gastric varices haemorrhage	1 (4.3)	0	0	0
Hepatic cirrhosis	0	0	1 (4.5)	1 (2.3)
Hepatosplenomegaly	0	0	1 (4.5)	1 (2.3)
Non-alcoholic fatty liver	0	0	1 (4.5)	1 (2.3)
Varices oesophageal	0	0	1 (4.5)	1 (2.3)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: A TEAE was defined as any AE starting or worsening on or after the first dose of the study drug.
Note: For the summarization of number of patients (n), a patient was counted only once for each preferred term even if > 1 event was reported.
Note: AEs were classified according to MedDRA Version 26.0.
Abbreviations: AE = adverse event; FMQ = FDA MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; OAEI = other adverse event of interest; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event

Potential cases of hepatic impairment were also examined by evaluation of laboratory parameters.

Mean values over time and percent change from Baseline for ALT, AST, total bilirubin, and ALP were within reference range at all time points and did not show any clinically meaningful trends. No patient in any treatment group met the criteria for Hy's law. Summary of abnormal post baseline liver function test in CS3 provided below under "Pool 4".

Table 64: Study CS3: Summary of Shift in CTCAE Grades from Baseline to Worst (Maximum) Post-Baseline Liver Function Test (Safety Set)

Treatment Group/ Liver Function Test	Baseline Grade	Worst (Maximum) Post-Baseline			
ALT, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal
Olezarsen 80 mg	≤ ULN	16 (72.7)	3 (13.6)	0	0
	> ULN-3.0 × ULN	1 (4.5)	2 (9.1)	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0

Treatment Group/ Liver Function Test	Baseline Grade	Worst (Maximum) Post-Baseline			
Olezarsen 50 mg	≤ ULN	16 (76.2)	5 (23.8)	0	0
	> ULN-3.0 × ULN	0	0	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Placebo	≤ ULN	17 (73.9)	3 (13.0)	1 (4.3)	0
	> ULN-3.0 × ULN	1 (4.3)	0	1 (4.3)	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
AST, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal;	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal;	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal.
Olezarsen 80 mg	≤ ULN	14 (63.6)	6 (27.3)	0	0
	> ULN-3.0 × ULN	0	2 (9.1)	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Olezarsen 50 mg	≤ ULN	14 (66.7)	4 (19.0)	0	0
	> ULN-3.0 × ULN	2 (9.5)	0	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Placebo	≤ ULN	16 (69.6)	6 (26.1)	1 (4.3)	0
	> ULN-3.0 × ULN	0	0	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Total Bilirubin, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-1.5 × ULN if Baseline normal (or missing) or > 1.0-1.5 × Baseline if Baseline abnormal	> 1.5-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal	> 3.0 × ULN if Baseline normal (or missing) or > 3.0 × Baseline if Baseline abnormal.
Olezarsen 80 mg	≤ ULN	17 (77.3)	4 (18.2)	0	0
	> ULN-1.5 × ULN	1 (4.5)	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0
Olezarsen 50 mg	≤ ULN	15 (71.4)	5 (23.8)	0	0
	> ULN-1.5 × ULN	1 (4.8)	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0
Placebo	≤ ULN	20 (87.0)	3 (13.0)	0	0
	> ULN-1.5 × ULN	0	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0

Note: N = number of safety patients in each treatment group; n = number of patients with result in specified category; % = n/N × 100.

Note: Baseline was defined as the last non-missing assessment prior to the first dose of study drug. If a patient had a Baseline value but had no post-Baseline values, then the worst value was labeled as "unknown". If a patient had a missing Baseline value but had a post-Baseline value, then the Baseline assessment was labeled as "unknown".

Note: Toxicity grades were based on CTCAE Version 5.0, November 2017.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

Pool 1 (CS3 + CS8)

Table 65: Summary of Treatment-emergent Abnormal Liver Function OAEI by Hepatic Injury FMQ (Narrow) by Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8			
		Olezarsen		
	Placebo (N = 62)	**50 mg (N = 79)**	**80 mg (N = 79)**	**Total Olezarsen (N = 158)**
Patients with at least one Treatment-emergent Adverse Events by Hepatic Injury FMQ (Narrow), n (%)	**3 (4.4)**	**4 (4.8)**	**5 (6.4)**	**9 (5.6)**
Alanine aminotransferase increased	1 (1.3)	3 (3.6)	4 (5.0)	7 (4.3)
Aspartate aminotransferase increased	1 (1.3)	1 (1.2)	2 (2.6)	3 (1.9)
Gastric varices	1 (1.3)	0	0	0
Gastric varices haemorrhage	1 (1.3)	0	0	0
Hepatic cirrhosis	0	0	1 (1.4)	1 (0.7))
Hepatomegaly	1 (1.8)	0	0	0
Hepatosplenomegaly	0	0	1 (1.4)	1 (0.7)
Non-alcoholic fatty liver	0	0	1 (1.4)	1 (0.7)
Non-alcoholic steatohepatitis	0	1 (1.2)	0	1 (0.6)
Varices oesophageal	0	0	1 (1.4)	1 (0.7)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For the summarization of number of patients (n), a patient was counted only once for each preferred term even if > 1 event was reported.
Note: MedDRA Version 26.0 was applied.
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; FMQ = FDA MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; OAEI = other adverse event of interest; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event.

Potential cases of hepatic impairment were also examined by evaluation of laboratory parameters.

Table 66: Summary of Abnormal Post-Baseline Liver Function Test Results (Pool 1)

	Pool 1 Study CS3 + Study CS8			
		Olezarsen		
Liver Function Test Abnormality Any time after first dose, n (%)	**Placebo (N = 62)**	**Olezarsen 50 mg (N = 79)**	**Olezarsen 80 mg (N = 79)**	**Total Olezarsen (N = 158)**
ALT ≥ ULN	8 (11.1)	33 (40.8)	27 (33.7)	60 (37.3)
ALT ≥ Max (3 ×ULN, 2 × Baseline)	2 (2.7)	4 (4.8)	1 (1.2)	5 (3.0)
ALT ≥ 3 × ULN	2 (2.7)	4 (4.8)	1 (1.2)	5 (3.0)
ALT ≥ 5 × ULN	1 (1.3)	2 (2.4)	0	2 (1.2)
ALT ≥ 8 × ULN	0	0	0	0
Highest Post-Baseline ALT Value				
ALT ≥ 3 × ULN - < 5 × ULN	1 (1.3)	2 (2.4)	1 (1.2)	3 (1.8)
ALT ≥ 5 × ULN - < 10 × ULN	1 (1.3)	2 (2.4)	0	2 (1.2)

Liver Function Test Abnormality Any time after first dose, n (%)	Pool 1 Study CS3 + Study CS8			
		Olezarsen		
	Placebo (N = 62)	Olezarsen 50 mg (N = 79)	Olezarsen 80 mg (N = 79)	Total Olezarsen (N = 158)
ALT ≥ 10 × ULN - < 20 × ULN	0	0	0	0
AST ≥ ULN	11 (16.4)	24 (30.3)	31 (39.1)	55 (34.7)
AST ≥ Max (3 ×ULN, 2 × Baseline)	1 (1.3)	3 (3.6)	1 (1.4)	4 (2.5)
AST ≥ 3 × ULN	1 (1.3)	3 (3.6)	1 (1.4)	4 (2.5)
AST ≥ 5 × ULN	0	1 (1.2)	0	1 (0.6)
AST ≥ 8 × ULN	0	0	0	0
Total bilirubin ≥ 2 × ULN	0	0	0	0
ALT ≥ 3 × ULN and Total Bilirubin ≥ 2 × ULN	0	0	0	0
AST ≥ 3 × ULN and Total Bilirubin ≥ 2 × ULN	0	0	0	0
ALT ≥ 3 × ULN and INR ≥ 1.5 × ULN	0	0	0	0
ALP ≥ 2 × ULN	1 (1.3)	0	0	0
ALP ≥ 3 × ULN	0	0	0	0
ALP ≥ 2 × ULN and (Baseline ALP < 2 × ULN or Baseline ALP missing)	1 (1.3)	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.
Note: Baseline for other parameters is defined as the last non-missing assessment prior to the first dose of study drug.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMH = Cochran-Mantel-Haenszel; INR = international normalized ratio; % = n/N * 100; ULN = upper limit of normal

To be noted, that olezarsen-treated patients in Study CS8 demonstrated a higher incidence of increases in ALT or AST than patients in the placebo group; these increases were mild, and mean changes were within reference range and not clinically meaningful. However, the patient population in Study CS8 included a higher proportion of patients with Type 2 diabetes mellitus, patients who were older and whose median BMI was in the obese range, compared with Study CS3; these characteristics place the CS8 population at a higher risk for hepatic steatosis. Therefore, liver function tests observations in the CS8 populations may not be directly relevant to the FCS population.

Table 67: Summary of Shift in Toxicity Grades from Baseline to Maximum Post-Baseline Liver Function Test (Pool 1)

Treatment Group/ Liver Function Test	Baseline Grade	Maximum Post-Baseline			
ALT, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal
Olezarsen 80 mg	≤ ULN	51 (64.9)	21 (26.1)	0	0
	> ULN-3.0 × ULN	4 (5.0)	3 (4.0)	0	0
	> 3.0-5.0 × ULN	0	0	0	0

Treatment Group/ Liver Function Test	Baseline Grade	Maximum Post-Baseline			
	> 5.0 × ULN	0	0	0	0
Olezarsen 50 mg	≤ ULN	45 (58.0)	26 (32.4)	0	2 (2.4)
	> ULN-3.0 × ULN	2 (2.4)	4 (4.8)	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Placebo	≤ ULN	53 (86.7)	4 (5.8)	1 (1.3)	0
	> ULN-3.0 × ULN	3 (4.9)	0	1 (1.3)	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
AST, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal;	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal;	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal.
Olezarsen 80 mg	≤ ULN	51 (64.5)	22 (27.8)	0	0
	> ULN-3.0 × ULN	1 (1.2)	5 (6.4)	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Olezarsen 50 mg	≤ ULN	54 (68.3)	17 (21.4)	1 (1.2)	1 (1.2)
	> ULN-3.0 × ULN	2 (2.9)	2 (2.4)	1 (1.2)	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
	Unknown	1 (1.5)	-	-	-
Placebo	≤ ULN	50 (81.8)	9 (13.3)	1 (1.3)	0
	> ULN-3.0 × ULN	2 (3.6)	0	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Total Bilirubin, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-1.5 × ULN if Baseline normal (or missing) or > 1.0-1.5 × Baseline if Baseline abnormal	> 1.5-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal	> 3.0 × ULN if Baseline normal (or missing) or > 3.0 × Baseline if Baseline abnormal.
Olezarsen 80 mg	≤ ULN	70 (88.2)	6 (8.0)	0	0
	> ULN-1.5 × ULN	1 (1.4)	2 (2.4)	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0
Olezarsen 50 mg	≤ ULN	71 (88.8)	7 (9.7)	0	0
	> ULN-1.5 × ULN	1 (1.5)	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0
Placebo	≤ ULN	57 (92.4)	4 (5.8)	0	0

Treatment Group/ Liver Function Test	Baseline Grade	Maximum Post-Baseline			
	> ULN-1.5 × ULN	0	0	1 (1.8)	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category.
Note: Pooled proportions are adjusted by study using CMH approach. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.
Note: Baseline was defined as the last non-missing assessment prior to the first dose of study drug. If a patient had a Baseline value but had no post-Baseline values, then the worst value was labeled as "unknown". If a patient had a missing Baseline value but had a post-Baseline value, then the Baseline assessment was labeled as "unknown".
Note: Toxicity grades were based on CTCAE Version 5.0, November 2017.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMH = Cochran-Mantel-Haenszel; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Table 68: Hepatic Impairment TEAE + Summary of Abnormal Liver Function TEAE by Hepatic Injury FMQ (Narrow) (CS3, CS8, and Pool 1)

	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
System Organ Class Preferred Term	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Any abnormal liver function TEAEs	2 (8.7)	0	2 (9.1)	2 (4.7)	1 (2.6)	4 (6.9)	3 (5.3)	7 (6.1)	3 (4.4)	4 (4.8)	5 (6.4)	9 (5.6)
Investigations												
Alanine aminotransferase increased	1 (4.3)	0	1 (4.5)	1 (2.3)	0	3 (5.2)	3 (5.3)	6 (5.2)	1 (1.3)	3 (3.6)	4 (5.0)	7 (4.3)
Aspartate aminotransferase increased	1 (4.3)	0	1 (4.5)	1 (2.3)	0	1 (1.7)	1 (1.8)	2 (1.7)	1 (1.3)	1 (1.2)	2 (2.6)	3 (1.9)
Hepatobiliary disorders												
Hepatic cirrhosis	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Hepatosplenomegaly	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Non-alcoholic fatty liver	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Non-alcoholic steatohepatitis	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Hepatomegaly	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0	0	0
Gastrointestinal disorders												
Varices oesophageal	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Gastric varices	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Gastric varices haemorrhage	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Any serious abnormal liver function TEAEs	--	--	--	--	--	--	--	--	1 (1.3)	0	1 (1.4)	1 (0.7)
Hepatobiliary disorders												
Hepatic cirrhosis	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Gastrointestinal disorders												
Gastric varices	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Gastric varices haemorrhage	1 (4.3)	0	0	0	0	0	0	0	1 (1.3)	0	0	0
Any fatal abnormal liver function TEAEs	0	0	0	0	0	0	0	0	0	0	0	0
Any abnormal liver function TEAEs with outcome of drug discontinuation	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Investigations												
Liver function test increased	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8).
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for ISIS 678354-CS3 and ISIS 678354-CS8, respectively.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.
Note: MedDRA Version 26.0 was applied.
Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; FMQ = FDA MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; N = number of safety patients in treatment group; n = number of patients in the specified category; TEAE = treatment-emergent adverse event.

Pool 4 (CS3 + CS13 + CS7)

No patients died due to an abnormal liver function OAEIs by Hepatic Injury FMQ (narrow). One (1.5%) patient in the olezarsen 80 mg from Study CS13 experienced an abnormal liver function OAEI with outcome of drug discontinuation.

Table 69 Summary of *Treatment-emergent Abnormal Liver Function OAEI by Hepatic Injury FMQ (Narrow) by Preferred Term (Pool 4)*

	Pool 4 Study CS3 + Study CS7 + Study CS13			
		Olezarsen		
	Placebo (N = 23)	**Olezarsen 50 mg/80 mg (N = 21)**	**Olezarsen 80 mg (N = 66)**	**Total Olezarsen (N = 87)**
Patients with at least one Treatment-emergent Adverse Event by Hepatic Injury FMQ (Narrow), n (%)	**2 (8.7)**	**0**	**3 (4.5)**	**3 (3.4)**
Alanine aminotransferase increased	1 (4.3)	0	2 (3.0)	2 (2.3)
Aspartate aminotransferase increased	1 (4.3)	0	2 (3.0)	2 (2.3)
Gastric varices	1 (4.3)	0	0	0
Gastric varices haemorrhage	1 (4.3)	0	0	0
Hepatic cirrhosis	0	0	1 (1.5)	1 (1.1)
Hepatosplenomegaly	0	0	1 (1.5)	1 (1.1)
Non-alcoholic fatty liver	0	0	1 (1.5)	1 (1.1)
Varices oesophageal	0	0	1 (1.5)	1 (1.1)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The olezarsen 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to olezarsen 80 mg and then had their dose reduced to 50 mg.
Note: MedDRA Version 26.0 was applied.
Abbreviations: AE = adverse event; FMQ = FDA MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; OAEI = other adverse event of interest; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event.

Table 70: Summary of Abnormal Post-Baseline Liver Function Test Results (CS3 and Pool 4)

Liver Function Test Abnormality Any time after first dose, n (%)	Study CS3				Pool 4 Study (CS3, CS7, CS13)			
		Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 23)	50 mg/80 mg (N = 21)	80 mg (N = 66)	Total Olezarsen (N = 87)
ALT ≥ ULN	7 (30.4)	5 (23.8)	5 (22.7)	10 (23.3)	7 (30.4)	7 (33.3)	16 (24.2)	23 (26.4)
ALT ≥ Max (3 ×ULN, 2 × Baseline)	2 (8.7)	0	0	0	2 (8.7)	0	0	0
ALT ≥ 3 × ULN	2 (8.7)	0	0	0	2 (8.7)	0	0	0
ALT ≥ 5 × ULN	1 (4.3)	0	0	0	1 (4.3)	0	0	0
ALT ≥ 8 × ULN	0	0	0	0	0	0	0	0
Highest Post-Baseline ALT Value [a]								
ALT ≥ 3 × ULN - < 5 × ULN	1 (4.3)	0	0	0	1 (4.3)	0	0	0
ALT ≥ 5 × ULN - < 10 × ULN	1 (4.3)	0	0	0	1 (4.3)	0	0	0
ALT ≥ 10 × ULN - < 20 × ULN	0	0	0	0	0	0	0	0
AST ≥ ULN	7 (30.4)	6 (28.6)	8 (36.4)	14 (32.6)	7 (30.4)	7 (33.3)	16 (24.2)	23 (26.4)
AST ≥ Max (3 ×ULN, 2 × Baseline)	1 (4.3)	0	1 (4.5)	1 (2.3)	1 (4.3)	0	1 (1.5)	1 (1.1)
AST ≥ 3 × ULN	1 (4.3)	0	1 (4.5)	1 (2.3)	1 (4.3)	0	1 (1.5)	1 (1.1)
AST ≥ 5 × ULN	0	0	0	0	0	0	0	0
Total bilirubin ≥ 2 × ULN	0	0	0	0	0	0	0	0
ALT ≥ 3 × ULN and Total Bilirubin ≥ 2 × ULN	0	0	0	0	0	0	0	0
AST ≥ 3 × ULN and Total Bilirubin ≥ 2 × ULN	0	0	0	0	0	0	0	0
ALT ≥ 3 × ULN and INR ≥ 1.5 × ULN	0	0	0	0	0	0	0	0
ALP ≥ 2 × ULN	1 (4.3)	0	0	0	1 (4.3)	0	1 (1.5)	1 (1.1)
ALP ≥ 3 × ULN	0	0	0	0	0	0	0	0
ALP ≥ 2 × ULN and (Baseline ALP < 2 × ULN or Baseline ALP missing)	1 (4.3)	0	0	0	1 (4.3)	0	0	0

Note: Patients who took placebo in ISIS 678354-CS3 then took olezarsen in ISIS 678354-CS13 were included in both placebo and active treatment groups.
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.

Table 71: Summary of Shift in Toxicity Grades from Baseline to Maximum Post-Baseline Liver Function Test (Pool 4)

Treatment Group/ Liver Function Test	**Baseline Grade**	**Maximum Post-Baseline**			
ALT, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal
Olezarsen 80 mg	≤ ULN	49 (74.2)	13 (19.7)	0	0
	> ULN-3.0 × ULN	2 (3.0)	2 (3.0)	0	0
	> 3.0-5.0 × ULN;	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Olezarsen 50 mg/80 mg	≤ ULN	14 (66.7)	7 (33.3)	0	0
	> ULN-3.0 × ULN	0	0	0	0
	> 3.0-5.0 × ULN;	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Placebo	≤ ULN	17 (73.9)	3 (13.0)	1 (4.3)	0
	> ULN-3.0 × ULN	1 (4.3)	0	1 (4.3)	0
	> 3.0-5.0 × ULN;	0	0	0	0
	> 5.0 × ULN	0	0	0	0
AST, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal;	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal;	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal.
Olezarsen 80 mg	≤ ULN	50 (75.8)	12 (18.2)	0	0
	> ULN-3.0 × ULN	1 (1.5)	2 (3.0)	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
	Unknown	-	1 (1.5)	-	-
AST, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal;	> 3.0-5.0 × ULN if Baseline normal (or missing) or > 3.0-5.0 × Baseline if Baseline abnormal;	> 5.0 × ULN if Baseline normal (or missing) or > 5.0 × Baseline if Baseline abnormal.
Olezarsen 50 mg/80 mg	≤ ULN	13 (61.9)	5 (23.8)	0	0
	> ULN-3.0 × ULN	1 (4.8)	1 (4.8)	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
	Unknown	1 (4.8)	-	-	-
Placebo	≤ ULN	16 (69.6)	6 (26.1)	1 (4.3)	0

Treatment Group/ Liver Function Test	Baseline Grade	Maximum Post-Baseline			
	> ULN-3.0 × ULN	0	0	0	0
	> 3.0-5.0 × ULN	0	0	0	0
	> 5.0 × ULN	0	0	0	0
Total Bilirubin, n (%)		≤ ULN or non-missing lab values that did not meet the criteria for mild, moderate or severe	> ULN-1.5 × ULN if Baseline normal (or missing) or > 1.0-1.5 × Baseline if Baseline abnormal	> 1.5-3.0 × ULN if Baseline normal (or missing) or > 1.5-3.0 × Baseline if Baseline abnormal	> 3.0 × ULN if Baseline normal (or missing) or > 3.0 × Baseline if Baseline abnormal.
Olezarsen 80 mg	≤ ULN	59 (89.4)	6 (9.1)	0	0
	> ULN-1.5 × ULN	1 (1.5)	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0
Olezarsen 50 mg/80 mg	≤ ULN	14 (66.7)	6 (28.6)	0	0
	> ULN-1.5 × ULN	1 (4.8)	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0
Placebo	≤ ULN	20 (87.0)	3 (13.0)	0	0
	> ULN-1.5 × ULN	0	0	0	0
	> 1.5-3.0 × ULN	0	0	0	0
	> 3.0 × ULN	0	0	0	0

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category, % = n/N × 100.
Note: Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to receiving the first dose of olezarsen or placebo. For patients who received olezarsen in CS3 and rolled over to CS13, the data from both CS3 and CS13 will be analyzed together. The Index Study Baseline will be used as the Baseline. For patients who received placebo in CS3 and rolled over to CS13, the Baseline was defined as the last non-missing assessment (including scheduled and unscheduled central lab assessments) prior to the first dose of olezarsen in CS13.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group. For patients who received olezarsen in CS3 and rolled over to CS13, the data from both CS3 and CS13 will be analyzed together.
Note: The olezarsen 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to olezarsen 80 mg and then had their dose reduced to 50 mg.
Note: If a patient had a Baseline value but had no post-Baseline values, then the maximum value was labeled as 'Unknown'. If a patient had a missing Baseline value but had a post-Baseline value, then the Baseline assessment was labeled as 'Unknown'.
Note: Toxicity grades were based on CTCAE Version 5.0, November 2017.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; FCS = familial chylomicronemia syndrome; ULN = upper limit of normal.

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Table 72: Summary of Treatment-emergent Abnormal Liver Function OAEI by Hepatic Injury FMQ (Narrow) by Preferred Term (Pool 5)

	Pool 5 Study CS2 + Study CS3 + Study CS7 + Study CS8 + Study CS13				
		Olezarsen			
	Placebo (N = 86)	10-40 mg (N = 68)	50 mg/80 mg (N = 101)	80 mg (N = 79)	Total Olezarsen (N = 248)
Patients with at least one TEAE by Hepatic Injury FMQ (Narrow), n (%)	**4 (4.7)**	**1 (1.5)**	**4 (4.0)**	**6 (4.9)**	**11 (3.8)**
Alanine aminotransferase increased	1 (1.2)	1 (1.5)	3 (3.0)	5 (4.1)	9 (3.1)
Aspartate aminotransferase increased	1 (1.2)	0	1 (1.0)	3 (2.4)	4 (1.4)
Gastric varices	1 (1.2)	0	0	0	0
Gastric varices haemorrhage	1 (1.2)	0	0	0	0
Hepatic cirrhosis	0	0	0	1 (0.8)	1 (0.3)
Hepatomegaly	1 (1.2)	0	0	0	0
Hepatosplenomegaly	0	0	0	1 (0.8)	1 (0.3)
Non-alcoholic fatty liver	0	0	0	1 (0.8)	1 (0.3)
Non-alcoholic steatohepatitis	1 (1.2)	0	1 (1.0)	0	1 (0.3)
Varices oesophageal	1 (1.2)	0	0	1 (0.8)	1 (0.3)

In Pool 5, mean hepatic transaminase levels remained within the reference range across all treatment groups throughout the study. There were no cases of Hy's law identified in any treatment group.

Table 73: Summary of Abnormal Post-Baseline Liver Function Test Results (Pool 5)

	Pool 5 Study CS2 + Study CS3 + Study CS7 + Study CS8 + Study CS13				
		Olezarsen			
Liver Function Test Abnormality Any time after first dose, n (%)	**Placebo (N = 86)**	**10-40 mg (N = 68)**	**50 mg/80 mg (N = 101)**	**80 mg (N = 123)**	**Total Olezarsen (N = 292)**
ALT ≥ ULN	20 (23.3)	29 (42.6)	45 (44.6)	38 (30.9)	112 (38.4)
ALT ≥ Max (3 × ULN, 2 × Baseline)	2 (2.3)	0	4 (4.0)	1 (0.8)	5 (1.7)
ALT ≥ 3 × ULN	2 (2.3)	0	4 (4.0)	1 (0.8)	5 (1.7)
ALT ≥ 5 × ULN	1 (1.2)	0	2 (2.0)	0	2 (0.7)
ALT ≥ 8 × ULN	0	0	0	0	0
Highest Post-Baseline ALT Value					
ALT ≥ 3 × ULN - < 5 × ULN	1 (1.2)	0	0	0	0
ALT ≥ 5 × ULN - < 10 × ULN	1 (1.2)	0	2 (2.0)	0	2 (0.7)
ALT ≥ 10 × ULN - < 20 × ULN	0	0	0	0	0
AST ≥ ULN	22 (25.6)	20 (29.4)	32 (31.7)	39 (31.7)	91 (31.2)
AST ≥ Max (3 ×ULN, 2 × Baseline)	1 (1.2)	1 (1.5)	3 (3.0)	1 (0.8)	5 (1.7)
AST ≥ 3 × ULN	1 (1.2)	1 (1.5)	3 (3.0)	1 (0.8)	5 (1.7)
AST ≥ 5 × ULN	0	0	1 (1.0)	0	1 (0.3)
AST ≥ 8 × ULN	0	0	0	0	0
Total bilirubin ≥ 2 × ULN	0	0	0	0	0
ALT ≥ 3 × ULN and Total Bilirubin ≥ 2 × ULN	0	0	0	0	0

Liver Function Test Abnormality Any time after first dose, n (%)	Pool 5 Study CS2 + Study CS3 + Study CS7 + Study CS8 + Study CS13				
		Olezarsen			
	Placebo (N = 86)	10-40 mg (N = 68)	50 mg/80 mg (N = 101)	80 mg (N = 123)	Total Olezarsen (N = 292)
AST ≥ 3 × ULN and Total Bilirubin ≥ 2 × ULN	0	0	0	0	0
ALT ≥ 3 × ULN and INR ≥ 1.5 × ULN	1 (1.2)	0	1 (1.0)	0	1 (0.3)
ALP ≥ 2 × ULN	1 (1.2)	0	0	1 (0.8)	1 (0.3)
ALP ≥ 3 × ULN	0	0	0	0	0
ALP ≥ 2 × ULN and (Baseline ALP < 2 × ULN or Baseline ALP missing)	1 (1.2)	0	0	0	0

Dysglycaemia and Hypoglycaemia AEs

Study CS3

Table 74: Summary of Treatment-emergent Dysglycaemia-related Events by Preferred Term (Safety Set)

FMQ Preferred Term	Placebo (N = 23) n (%)	Olezarsen 50 mg (N = 21) n (%)	Olezarsen 80 mg (N = 22) n (%)	Total Olezarsen (N = 43) n (%)
Patients with at least one TEAE by Dysglycaemia-related FMQ (Broad)	**4 (17.4)**	**2 (9.5)**	**2 (9.1)**	**4 (9.3)**
Hypoglycaemia				
Hypoglycaemia	2 (8.7)	1 (4.8)	1 (4.5)	2 (4.7)
Hyperglycaemia				
Blood glucose increased	1 (4.3)	1 (4.8)	0	1 (2.3)
Pancreatogenous diabetes	1 (4.3)	0	0	0
Type 2 diabetes mellitus	1 (4.3)	0	0	0
Type 3 diabetes mellitus	0	0	1 (4.5)	1 (2.3)
Diabetic Ketoacidosis	0	0	0	0

Among the 50 patients with no history of diabetes, the proportion of patients fulfilling ≥ 1 hyperglycaemia algorithmic FMQ criteria was greater in both the olezarsen 80 mg group (53.3%) and the olezarsen 50 mg group (50.0%) compared with the placebo group (35.3%). The most commonly fulfilled criteria in this subgroup included "change from Baseline fasting glucose ≥ 20 mg/dL with post-Baseline fasting glucose > 100 mg/dL" (53.3%, 44.4%, and 23.5% in the olezarsen 80 mg, olezarsen 50 mg, and placebo groups, respectively) and "HbA1c Increase ≥ 0.3% with post-Baseline HbA1c ≥ 5.7%" (26.7%, 27.8%, and 11.8%, respectively).

As expected, all 16 patients with a history of diabetes fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria across treatment groups. The most commonly fulfilled criteria in this subgroup included " change from Baseline fasting glucose ≥ 20 mg/dL with post-Baseline fasting glucose > 100 mg/dL" (100%, 100%, and 66.7% in the olezarsen 80 mg, olezarsen 50 mg, and placebo groups, respectively), "fasting glucose ≥ 126 mg/dL" (57.1%, 100%, and 83.3%, respectively), and "post-Baseline HbA1c ≥ 6.5%" (42.9%%, 100%, and 66.7%, respectively).

The proportion of patients whose worst haemoglobin A1c value indicated diabetes (i.e., HbA1c ≥ 6.5%) was similar across treatment groups, i.e., 18.2%, 19.0%, and 21.7% in the olezarsen 80 mg group, olezarsen 50 mg group, and placebo group, respectively.

There was no clear pattern in blood glucose measurements across treatment groups. In the olezarsen 80 mg group, 18.2% of patients had a nadir glucose level < 54 mg/dL during the study, while 27.3% experienced either a peak fasting glucose level ≥ 126 mg/dL or peak random glucose ≥ 200 mg/dL. In the olezarsen 50 mg group, 33.3% of patients had a nadir glucose level < 54 mg/dL during the study, while 28.6% experienced either a peak fasting glucose level ≥ 126 mg/dL or peak random glucose ≥ 200 mg/dL. In the placebo group, 13.0% of patients had a nadir glucose level < 54 mg/dL during the study, while 21.7% experienced either a peak fasting glucose level ≥ 126 mg/dL or peak random glucose ≥ 200 mg/dL.

Pool 1 (CS3 + CS8)

A greater proportion of patients experienced dysglycaemia-related events (by dysglycaemia FMQ narrow and broad) in the placebo group (14.2% and 16.0%, respectively) compared with the olezarsen 80 mg group (9.9% and 11.3%, respectively) and the olezarsen 50 mg group (12.5% and 13.7%, respectively).

The proportion of patients whose worst haemoglobin A1c value indicated diabetes (i.e., HbA1c ≥ 6.5%) was slightly lower in the olezarsen 80 mg group (43.3%) and the olezarsen 50 mg group (46.5%) compared with the placebo group (52.9%).

Among the 99 patients with no history of diabetes, proportionally greater patients fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria in the olezarsen 50 mg group (53.3%) compared with the olezarsen 80 mg (43.3%) and the placebo (44.6%) group. The most commonly fulfilled criteria in this subgroup included "fasting glucose ≥ 20 mg/dL with post-Baseline fasting glucose > 100 mg/dL" (40.9%, 43.7%, and 38.3% in the olezarsen 80 mg, olezarsen 50 mg, and placebo groups, respectively) and "fasting glucose ≥ 126 mg/dL" (19.3%, 24.4%, and 20.5%, respectively).

Most all 121 patients with a history of diabetes fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria across treatment groups (95.4%, 95.2%, and 100% in the olezarsen 80 mg, olezarsen 50 mg, and placebo groups, respectively). The most commonly fulfilled criteria in this subgroup included "fasting glucose ≥ 126 mg/dL" (88.0%, 92.9%, and 95.1% in the olezarsen 80 mg, olezarsen 50 mg, and placebo groups, respectively), "post-Baseline HbA1c ≥ 6.5%" (72.3%, 85.7%, and 84.3%, respectively), and "fasting glucose ≥ 20 mg/dL with post-Baseline fasting glucose > 100 mg/dL" (74.5%, 80.9%, and 69.6%, respectively).

Regarding post-Baseline fasting glucose levels, 3 (4.0%), 6 (8.2%), and 9 (12.4%) patients had a fasting glucose ≥ 54 to < 70 mg/dL and 4 (5.6%), 8 (11.4%), and 3 (4.0%) patients had a fasting glucose < 54 mg/dL in the olezarsen 80 mg, olezarsen 50 mg, placebo groups, respectively. A greater proportion of patients in the olezarsen 80 mg and olezarsen 50 mg groups had a fasting glucose ≥ 100 to < 126 mg/dL compared with the placebo group (41.6%, 36.4%, and 20.0%, respectively). In contrast, fewer patients in the olezarsen treatment groups had a fasting glucose ≥ 126 mg/dL or a random glucose ≥ 200 mg/dL compared with patients in the placebo group (57.0%, 57.8%, and 65.3%, respectively). A similar pattern was observed for HbA1c ≥ 6.5% (43.3%, 46.5%, and 52.9%, respectively).

Pool 4 (CS3 + CS13 + CS7)

Across all FCS population trials, a lower proportion of patients experienced dysglycaemia-related events (by dysglycaemia FMQ narrow and broad) in the olezarsen 80 mg group (7.6% each) compared with the placebo group (17.4% each) and the olezarsen 50 mg/80 mg group (14.3% each).

Among the 79 patients with no history of diabetes, a greater proportion of patients fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria in the olezarsen 50 mg/80 mg group (55.6%) compared with the olezarsen 80 mg (43.2%), and the placebo group (35.3%).

As expected, all 31 patients with a history of diabetes fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria across treatment groups.

Regarding post-Baseline fasting glucose levels, 7 (10.6%), 4 (19.0%), and 8 (34.8%) patients had a fasting glucose ≥ 54 to < 70 mg/dL and 5 (7.6%), 7 (33.3%), and 3 (13.0%) patients had a fasting glucose < 54 mg/dL in the olezarsen 80 mg, olezarsen 50 mg/80 mg, and placebo groups, respectively. A greater proportion of patients in the olezarsen 80 mg and olezarsen 50 mg/80 mg groups had a fasting glucose ≥ 100 to < 126 mg/dL compared with the placebo group (40.9%, 52.4%, and 30.4%, respectively) and had a fasting glucose ≥ 126 mg/dL or a random glucose ≥ 200 mg/dL compared with patients in the placebo group (36.4%, 33.3%, and 21.7% respectively). A similar pattern was observed for HbA1c ≥ 6.5% (24.2%, 19.0%, and 21.7%, respectively).

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Overall, a lower proportion of patients experienced dysglycaemia-related events (by dysglycaemia FMQ narrow and broad) in the olezarsen 80 mg group (9.8% each) compared with the placebo group (14.0% and 16.3%, respectively), the olezarsen 50 mg/80 mg group (11.9% and 12.9%, respectively), and the olezarsen 10-40 mg group (13.2% each).

Among the 165 patients with no history of diabetes, proportionally greater patients fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria in the olezarsen 50 mg/80 mg group (57.1%) compared with the olezarsen 80 mg (39.7%), the olezarsen 10-40 mg group (40.0%), and the placebo group (45.5%).

As expected, nearly all 213 patients with a history of diabetes fulfilled ≥ 1 hyperglycaemia algorithmic FMQ criteria across treatment groups (96.7%, 96.2%, 100%, and 100% in the olezarsen 80 mg, olezarsen 50 mg/80 mg, olezarsen 10-40 mg, and placebo groups, respectively).

2.5.8.4. Laboratory findings

Changes over time in platelet counts, hepatic enzymes, bilirubin, creatinine, Urine albumin-creatinine ratio (UACR) and Urine protein-creatinine ratio (UPCR) are discussed in relevant parts of section 2.5.8.3.3. Other laboratory findings are discussed below. Regarding other findings, such as heart rate, respiratory rate, systolic and diastolic BP, body temperature, weight, BMI, or ECG - no clinically meaningful trends or safety concerns were observed across olezarsen clinical studies.

2.5.8.4.1. Haematology

Overall, 6 patients in the olezarsen 80 mg group experienced an adverse shift of ≥ 2 severity categories: 2 patients in haemoglobin levels and 4 patients in WBC count.

Overall, 5 patients in the olezarsen 50 mg/80 mg group experienced an adverse shift of ≥ 2 severity categories: 4 patients in haemoglobin levels and 1 patient in WBC count.

Overall, no patients in the olezarsen 10-40 mg group experienced an adverse shift of ≥ 2 severity categories.

Overall, 2 patients in the placebo group experienced an adverse shift of ≥ 2 severity categories in WBC count.

Laboratory trends related to hematologic and other parameters for the individual clinical studies and integrated pools were consistent with the AE patterns. No notable trends or additional safety concerns were observed.

2.5.8.4.2. Chemistry

Study CS3

Three patients in the olezarsen 80 mg group experienced adverse shift of ≥ 2 severity categories in LDL-C values; none were receiving concomitant LDL-C lowering medication from Baseline. No patients in the olezarsen 50 mg and placebo groups experienced such adverse shift.

Pool 1 (CS3 + CS8)

Fifteen (18.7%) patients in the olezarsen 80 mg group, 14 (16.8%) patients in the olezarsen 50 mg group, and 13 (23.0%) patients in the placebo group experienced an adverse shift of ≥ 2 severity categories in LDL-C values.

Pool 4 (CS3 + CS13 + CS7)

Six (9.0%) patients in the olezarsen 80 mg group experienced an adverse shift of ≥ 2 severity categories in LDL C values.

Laboratory trends related to chemistry for the individual clinical studies and integrated pools were consistent with the AE patterns. No other notable trends or additional safety concerns were observed.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Intrinsic Factors

Gender

Pool 1 (CS3 + CS8)

Table 75: Differences in Treatment-emergent Adverse Events by Gender by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		**Olezarsen 50 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	Female (n = 36)	**Male (n = 26)**	**Female (n = 39)**	**Male (n = 40)**	**Female (n = 28)**	**Male (n = 51)**	**Female (n = 67)**	**Male (n = 91)**
Patients with Any TEAE	29 (80.6)	23 (88.5)	29 (74.4)	32 (80.0)	21 (75.0)	36 (70.6)	50 (74.6)	68 (74.7)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	8 (22.2)	9 (34.6)	7 (17.9)	6 (15.0)	12 (42.9)	6 (11.8)	19 (28.4)	12 (13.2)
General disorders and administration site conditions	7 (19.4)	5 (19.2)	14 (35.9)	7 (17.5)	8 (28.6)	6 (11.8)	22 (32.8)	13 (14.3)
Nervous system disorders	7 (19.4)	4 (15.4)	9 (23.1)	3 (7.5)	5 (17.9)	4 (7.8)	14 (20.9)	7 (7.7)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	4 (11.1)	4 (15.4)	4 (10.3)	0	5 (17.9)	1 (2.0)	9 (13.4)	1 (1.1)
Urinary tract infection	6 (16.7)	0	8 (20.5)	1 (2.5)	4 (14.3)	0	12 (17.9)	1 (1.1)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Pool 4 (CS3 + CS13 + CS7)

Table 76: Differences in Treatment-emergent Adverse Events by Gender by System Organ Class and Preferred Term (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		**Olezarsen 50 mg/80 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	Female (n = 12)	**Male (n = 11)**	**Female (n = 15)**	**Male (n = 6)**	**Female (n = 35)**	**Male (n = 31)**	**Female (n = 50)**	**Male (n = 37)**
Patients with Any TEAE	11 (91.7)	11 (100.0)	13 (86.7)	6 (100.0)	32 (91.4)	26 (83.9)	45 (90.0)	32 (86.5)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	7 (58.3)	9 (81.8)	5 (33.3)	2 (33.3)	25 (71.4)	8 (25.8)	30 (60.0)	10 (27.0)
Nervous system disorders	4 (33.3)	2 (18.2)	8 (53.3)	1 (16.7)	8 (22.9)	6 (19.4)	16 (32.0)	7 (18.9)
Psychiatric disorders	1 (8.3)	1 (9.1)	4 (26.7)	2 (33.3)	4 (11.4)	0	8 (16.0)	2 (5.4)
Respiratory, thoracic and mediastinal disorders	3 (25.0)	2 (18.2)	5 (33.3)	2 (33.3)	10 (28.6)	4 (12.9)	15 (30.0)	6 (16.2)
Skin and subcutaneous tissue disorders	3 (25.0)	2 (18.2)	4 (26.7)	1 (16.7)	5 (14.3)	1 (3.2)	9 (18.0)	2 (5.4)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	4 (33.3)	4 (36.4)	3 (20.0)	0	10 (28.6)	5 (16.1)	13 (26.0)	5 (13.5)
Abdominal pain upper	1 (8.3)	0	2 (13.3)	0	4 (11.4)	0	6 (12.0)	0
Diarrhoea	2 (16.7)	4 (36.4)	1 (6.7)	0	5 (14.3)	0	6 (12.0)	0
Nausea	0	1 (9.1)	1 (6.7)	1 (16.7)	7 (20)	0	8 (16.0)	1 (2.7)
Type 2 diabetes mellitus	0	1 (9.1)	0	2 (33.3)	0	2 (6.5)	0	4 (10.8)
Urinary tract infection	0	0	3 (20.0)	0	2 (5.7)	0	5 (10.0)	0

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The ISIS-678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS-678354 80 mg and then had their dose reduced to 50 mg.

Race

Some differences were observed in non-white vs white patients groups regarding AEs, however, no meaningful conclusions can be drawn due to very limited number of non-white patient population (6 to 10 in Pool 1 patient groups and 1 to 9 in Pool 4 patient groups).

Ethnicity

Pool 1 (CS3 + CS8)

Table 77: Differences in Treatment-emergent Adverse Events by Ethnicity by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		**Olezarsen 50 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	Hispanic/ Latino (n = 16)	**Not Hispanic/ Latino (n = 46)**	**Hispanic/ Latino (n = 24)**	**Not Hispanic/ Latino (n = 55)**	**Hispanic/ Latino (n = 24)**	**Not Hispanic/ Latino (n = 55)**	**Hispanic/ Latino (n = 48)**	**Not Hispanic/ Latino (n = 110)**
Patients with Any TEAE	10 (62.5)	42 (91.3)	14 (58.3)	47 (85.5)	12 (50.0)	45 (81.8)	26 (54.2)	92 (83.6)
System Organ Classes with ≥ 10% Difference Between Subgroups								

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		Olezarsen 50 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	Hispanic/ Latino (n = 16)	Not Hispanic/ Latino (n = 46)	Hispanic/ Latino (n = 24)	Not Hispanic/ Latino (n = 55)	Hispanic/ Latino (n = 24)	Not Hispanic/ Latino (n = 55)	Hispanic/ Latino (n = 48)	Not Hispanic/ Latino (n = 110)
General disorders and administration site conditions	2 (12.5)	10 (21.7)	4 (16.7)	17 (30.9)	0	14 (25.5)	4 (8.3)	31 (28.2)
Infections and infestations	3 (18.8)	28 (60.9)	4 (16.7)	30 (54.5)	2 (8.3)	22 (40.0)	6 (12.5)	52 (47.3)
Musculoskeletal and connective tissue disorders	1 (6.3)	10 (21.7)	4 (16.7)	18 (32.7)	2 (8.3)	8 (14.5)	6 (12.5)	26 (23.6)
Preferred Terms with ≥ 10% Difference Between Subgroups								
COVID-19	0	10 (21.7)	0	11 (20.0)	0	7 (12.7)	0	18 (16.4)

Results in Pool 4 will not be discussed due to very limited number of Hispanic/Latino patient population (3 patients in every group of mentioned pool).

Weight

Pool 1 (CS3 + CS8)

In Pool 1, the incidence of TEAEs between weight quartile group for the total olezarsen group (50 mg and 80 mg groups combined) at Baseline was as follows:

- First Quartile (≤ Q1): 32 (80%) patients in the total olezarsen groups.
- Second Quartile (> Q1, ≤ Q2): 28 (66.7%) patients in the total olezarsen groups.
- Third Quartile (> Q2, ≤ Q3): 27 (77.1%) patients in the total olezarsen groups.
- Fourth Quartile (> Q3): 31 (75.6%) patients in the total olezarsen groups.

Table 78: Differences in Treatment-emergent Adverse Events by Weight Category by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8															
	Placebo n (%)				**Olezarsen 50 mg n (%)**				**Olezarsen 80 mg n (%)**				**Total Olezarsen n (%)**			
	≥ Q1 (n = 15)	**> Q1, ≤ Q2 (n = 15)**	**> Q2, ≤ Q3 (n = 18)**	**> Q3 (n = 14)**	**≥ Q1 (n = 20)**	**> Q1, ≤ Q2 (n = 20)**	**> Q2, ≤ Q3 (n = 20)**	**> Q3 (n = 19)**	**≥ Q1 (n = 20)**	**> Q1, ≤ Q2 (n = 22)**	**> Q2, ≤ Q3 (n = 15)**	**> Q3 (n = 22)**	**≥ Q1 (n = 40)**	**> Q1, ≤ Q2 (n = 42)**	**> Q2, ≤ Q3 (n = 35)**	**> Q3 (n = 41)**
Patients with Any TEAE	13 (86.7)	13 (86.7)	14 (77.8)	12 (85.7)	16 (80.0)	15 (75.0)	15 (75.0)	15 (78.9)	16 (80.0)	13 (59.1)	12 (80.0)	16 (72.7)	32 (80.0)	28 (66.7)	27 (77.1)	31 (75.6)
System Organ Classes with ≥ 10% Difference Between Subgroups																
Blood and lymphatic system disorders	2 (13.3)	0	0	1 (7.1)	2 (10.0)	0	1 (5.0)	1 (5.3)	3 (15.0)	1 (4.5)	1 (6.7)	1 (4.5)	5 (12.5)	1 (2.4)	2 (5.7)	2 (4.9)
Gastrointestinal disorders	9 (60.0)	6 (40.0)	1 (5.6)	1 (7.1)	6 (30.0)	4 (20.0)	0	3 (15.8)	7 (35.0)	5 (22.7)	2 (13.3)	4 (18.2)	13 (32.5)	9 (21.4)	2 (5.7)	7 (17.1)
General disorders and administration site conditions	4 (26.7)	3 (20.0)	4 (22.2)	1 (7.1)	5 (25.0)	6 (30.0)	4 (20.0)	6 (31.6)	5 (25.0)	3 (13.6)	1 (6.7)	5 (22.7)	10 (25.0)	9 (21.4)	5 (14.3)	11 (26.8)
Metabolism and nutrition disorders	3 (20.0)	1 (6.7)	4 (22.2)	4 (28.6)	3 (15.0)	2 (10.0)	3 (15.0)	2 (10.5)	2 (10.0)	0	1 (6.7)	7 (31.8)	5 (12.5)	2 (4.8)	4 (11.4)	9 (22.0)
Musculoskeletal and connective tissue disorders	3 (20.0)	1 (6.7)	5 (27.8)	2 (14.3)	5 (25.0)	6 (30.0)	6 (30.0)	5 (26.3)	6 (30.0)	2 (9.1)	2 (13.3)	0	11 (27.5)	8 (19.0)	8 (22.9)	5 (12.2)
Nervous system disorders	4 (26.7)	2 (13.3)	3 (16.7)	2 (14.3)	8 (40.0)	2 (10.0)	2 (10.0)	0	3 (15.0)	2 (9.1)	1 (6.7)	3 (13.6)	11 (27.5)	4 (9.5)	3 (8.6)	3 (7.3)
Respiratory, thoracic and mediastinal disorders	4 (26.7)	1 (6.7)	2 (11.1)	2 (14.3)	5 (25.0)	2 (10.0)	5 (25.0)	1 (5.3)	4 (20.0)	4 (18.2)	0	2 (9.1)	9 (22.5)	6 (14.3)	5 (14.3)	3 (7.3)
Preferred Terms with ≥ 10% Difference Between Subgroups																
Abdominal pain	4 (26.7)	3 (20.0)	1 (5.6)	0	3 (15.0)	1 (5.0)	0	0	3 (15.0)	1 (4.5)	1 (6.7)	1 (4.5)	6 (15.0)	2 (4.8)	1 (2.9)	1 (2.4)
Abdominal pain upper	1 (6.7)	0	0	0	2 (10.0)	0	0	0	2 (10.0)	0	1 (6.7)	0	4 (10.0)	0	1 (2.9)	0
Alanine aminotransferase increased	0	1 (6.7)	0	0	0	3 (15.0)	0	0	4 (20.0)	0	0	0	4 (10.0)	3 (7.1)	0	0
Cough	2 (13.3)	0	2 (11.1)	0	2 (10.0)	0	1 (5.0)	0	3 (15.0)	1 (4.5)	0	1 (4.5)	5 (12.5)	1 (2.4)	1 (2.9)	1 (2.4)

	Pool 1 Study CS3 + Study CS8															
	Placebo n (%)				Olezarsen 50 mg n (%)				Olezarsen 80 mg n (%)				Total Olezarsen n (%)			
	≥ Q1 (n = 15)	> Q1, ≤ Q2 (n = 15)	> Q2, ≤ Q3 (n = 18)	> Q3 (n = 14)	≥ Q1 (n = 20)	> Q1, ≤ Q2 (n = 20)	> Q2, ≤ Q3 (n = 20)	> Q3 (n = 19)	≥ Q1 (n = 20)	> Q1, ≤ Q2 (n = 22)	> Q2, ≤ Q3 (n = 15)	> Q3 (n = 22)	≥ Q1 (n = 40)	> Q1, ≤ Q2 (n = 42)	> Q2, ≤ Q3 (n = 35)	> Q3 (n = 41)
Gamma-glutamyltransferase increased	1 (6.7)	0	0	0	1 (5.0)	2 (10.0)	0	0	3 (15.0)	0	0	0	4 (10.0)	2 (4.8)	0	0
Headache	1 (6.7)	1 (6.7)	1 (5.6)	1 (7.1)	3 (15.0)	2 (10.0)	0	0	1 (5.0)	1 (4.5)	1 (6.7)	0	4 (10.0)	3 (7.1)	1 (2.9)	0
Pain in extremity	1 (6.7)	0	0	0	1 (5.0)	1 (5.0)	1 (5.0)	0	3 (15.0)	1 (4.5)	1 (6.7)	0	4 (10.0)	2 (4.8)	2 (5.7)	0

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Results in Pool 4 will not be discussed due to very limited number of patients in different weight quartiles.

Baseline Diabetic Status

Pool 1 (CS3 + CS8)

Table 79: Differences in Treatment-emergent Adverse Events by Baseline Diabetic Status by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		**Olezarsen 50 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	Diabetic (n = 36)	**Not Diabetic (n = 26)**	**Diabetic (n = 40)**	**Not Diabetic (n = 39)**	**Diabetic (n = 45)**	**Not Diabetic (n = 34)**	**Diabetic (n = 85)**	**Not Diabetic (n = 73)**
Patients with Any TEAE	30 (83.3)	22 (84.6)	27 (67.5)	34 (87.2)	29 (64.4)	28 (82.4)	56 (65.9)	62 (84.9)
System Organ Classes with ≥ 10% Difference Between Subgroups								
General disorders and administration site conditions	5 (13.9)	7 (26.9)	8 (20.0)	13 (33.3)	5 (11.1)	9 (26.5)	13 (15.3)	22 (30.1)
Infections and infestations	16 (44.4)	15 (57.7)	14 (35.0)	20 (51.3)	11 (24.4)	13 (38.2)	25 (29.4)	33 (45.2)
Nervous system disorders	6 (16.7)	5 (19.2)	3 (7.5)	9 (23.1)	3 (6.7)	6 (17.6)	6 (7.1)	15 (20.5)
Respiratory, thoracic and mediastinal disorders	3 (8.3)	6 (23.1)	5 (12.5)	8 (20.5)	2 (4.4)	8 (23.5)	7 (8.2)	16 (21.9)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Pain in extremity	0	1 (3.8)	0	3 (7.7)	0	5 (14.7)	0	8 (11.0)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Pool 4 (CS3 + CS13 + CS7)

Table 80: Difference in Treatment-emergent Adverse Events by Baseline Diabetic Status and Treatment Group by System Organ Class and Preferred Term (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		**Olezarsen 50 mg/80 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	Diabetic (n = 6)	**Not Diabetic (n = 17)**	**Diabetic (n = 3)**	**Not Diabetic (n = 18)**	**Diabetic (n = 22)**	**Not Diabetic (n = 44)**	**Diabetic (n = 25)**	**Not Diabetic (n = 62)**
Patients with Any TEAE	6 (100.0)	16 (94.1)	2 (66.7)	17 (94.4)	20 (90.9)	38 (86.4)	22 (88.0)	55 (88.7)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	5 (83.3)	11 (64.7)	1 (33.3)	6 (33.3)	7 (31.8)	26 (59.1)	8 (32.0)	32 (51.6)
General disorders and administration site conditions	2 (33.3)	6 (35.3)	1 (33.3)	7 (38.9)	4 (18.2)	26 (59.1)	5 (20.0)	33 (53.2)
Infections and infestations	2 (33.3)	11 (64.7)	2 (66.7)	13 (72.2)	8 (36.4)	22 (50.0)	10 (40.0)	35 (56.5)
Investigations	1 (16.7)	3 (17.6)	1 (33.3)	2 (11.1)	5 (22.7)	6 (13.6)	6 (24.0)	8 (12.9)
Metabolism and nutrition disorders	2 (33.3)	3 (17.6)	2 (66.7)	3 (16.7)	3 (13.6)	3 (6.8)	5 (20.0)	6 (9.7)
Nervous system disorders	2 (33.3)	4 (23.5)	1 (33.3)	8 (44.4)	1 (4.5)	13 (29.5)	2 (8.0)	21 (33.9)
Psychiatric disorders	2 (33.3)	0	1 (33.3)	5 (27.8)	0	4 (9.1)	1 (4.0)	9 (14.5)
Skin and subcutaneous tissue disorders	2 (33.3)	3 (17.6)	0	5 (27.8)	1 (4.5)	5 (11.4)	1 (4.0)	10 (16.1)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	2 (33.3)	6 (35.3)	0	3 (16.7)	2 (9.1)	13 (29.5)	2 (8.0)	16 (25.8)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		Olezarsen 50 mg/80 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	Diabetic (n = 6)	Not Diabetic (n = 17)	Diabetic (n = 3)	Not Diabetic (n = 18)	Diabetic (n = 22)	Not Diabetic (n = 44)	Diabetic (n = 25)	Not Diabetic (n = 62)
Headache	1 (16.7)	2 (11.8)	0	4 (22.2)	0	8 (18.2)	0	12 (19.4)
Influenza	0	2 (11.8)	0	6 (33.3)	1 (4.5)	5 (11.4)	1 (4.0)	11 (17.7)
Injection site discolouration	0	1 (5.9)	0	1 (5.6)	0	7 (15.9)	0	8 (12.9)
Nasopharyngitis	0	1 (5.9)	0	4 (22.2)	0	4 (9.1)	0	8 (12.9)
Platelet count decreased	0	1 (5.9)	1 (33.3)	0	2 (9.1)	1 (2.3)	3 (12.0)	1 (1.6)
Type 2 diabetes mellitus	1 (16.7)	0	1 (33.3)	1 (5.6)	2 (9.1)	0	3 (12.0)	1 (1.6)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The ISIS-678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS-678354 80 mg and then had their dose reduced to 50 mg

Age

Pool 1 (CS3 + CS8)

In Pool 1, the incidence of TEAEs was similar in patients < 65 years of age (81 [75.7%]) and patients ≥ 65 years of age (37 [72.5%]) for the total olezarsen group (50 mg and 80 mg groups combined). Although there were TEAEs that had a higher incidence in one age group than in the other, the overall data are not suggestive of any meaningful trends or differences.

Table 81: Differences in Treatment-emergent Adverse Events by Age by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		Olezarsen 50 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	< 65 Years (n = 43)	≥ 65 Years (n = 19)	< 65 Years (n = 53)	≥ 65 Years (n = 26)	< 65 Years (n = 54)	≥ 65 Years (n = 25)	< 65 Years (n = 107)	≥ 65 Years (n = 51)
Patients with Any TEAE	37 (86.0)	15 (78.9)	42 (79.2)	19 (73.1)	39 (72.2)	18 (72.0)	81 (75.7)	37 (72.5)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Investigations	8 (18.6)	2 (10.5)	8 (15.1)	6 (23.1)	8 (14.8)	7 (28.0)	16 (15.0)	13 (25.5)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Pool 4 (CS3 + CS13 + CS7)

Table 82: Differences in Treatment-emergent Adverse Events by Age by System Organ Class and Preferred Term (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		**Olezarsen 50 mg/ 80 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	< 65 Years (n = 20)	**≥ 65 Years (n = 3)**	**< 65 Years (n = 20)**	**≥ 65 Years (n = 1)**	**< 65 Years (n = 60)**	**≥ 65 Years (n = 6)**	**< 65 Years (n = 80)**	**≥ 65 Years (n = 7)**
Patients with Any TEAE	19 (95.0)	3 (100.0)	18 (90.0)	1 (100.0)	52 (86.7)	6 (100.0)	70 (87.5)	7 (100.0)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	13 (65.0)	3 (100.0)	7 (35.0)	0	31 (51.7)	2 (33.3)	38 (47.5)	2 (28.6)
General disorders and administration site conditions	7 (35.0)	1 (33.3)	7 (35.0)	1 (100.0)	27 (45.0)	3 (50.0)	34 (42.5)	4 (57.1)
Hepatobiliary disorders	1 (5.0)	0	0	0	2 (3.3)	1 (16.7)	2 (2.5)	1 (14.3)
Infections and infestations	11 (55.0)	2 (66.7)	15 (75.0)	0	28 (46.7)	2 (33.3)	43 (53.8)	2 (28.6)
Metabolism and nutrition disorders	5 (25.0)	0	5 (25.0)	0	6 (10.0)	0	11 (13.8)	0
Musculoskeletal and connective tissue disorders	3 (15.0)	1 (33.3)	8 (40.0)	0	18 (30.0)	3 (50.0)	26 (32.5)	3 (42.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (5.0)	0	0	0	0	2 (33.3)	0	2 (28.6)
Nervous system disorders	6 (30.0)	0	9 (45.0)	0	14 (23.3)	0	23 (28.8)	0
Psychiatric disorders	2 (10.0)	0	6 (30.0)	0	4 (6.7)	0	10 (12.5)	0
Reproductive system and breast disorders	1 (5.0)	0	3 (15.0)	0	3 (5.0)	2 (33.3)	6 (7.5)	2 (28.6)
Respiratory, thoracic and mediastinal disorders	5 (25.0)	0	7 (35.0)	0	13 (21.7)	1 (16.7)	20 (25.0)	1 (14.3)
Vascular disorders	1 (5.0)	0	1 (5.0)	0	7 (11.7)	0	8 (10.0)	0
Preferred Terms with ≥ 10% Difference Between Subgroups								
Arthralgia	0	0	4 (20.0)	0	3 (5.0)	2 (33.3)	7 (8.8)	2 (28.6)
Basal cell carcinoma	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Breast pain	0	0	0	0	1 (1.7)	1 (16.7)	1 (1.3)	1 (14.3)
Chills	0	0	1 (5.0)	0	3 (5.0)	2 (33.3)	4 (5.0)	2 (28.6)
Coccydynia	0	0	1 (5.0)	0	0	1 (16.7)	1 (1.3)	1 (14.3)
Cough	2 (10.0)	0	3 (15.0)	0	6 (10.0)	0	9 (11.3)	0
COVID-19	8 (40.0)	0	10 (50.0)	0	13 (21.7)	0	23 (28.8)	0
Dry mouth	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Dyspnoea	1 (5.0)	0	0	0	0	1 (16.7)	0	1 (14.3)
Ejaculation failure	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Erectile dysfunction	0	0	1 (5.0)	0	1 (1.7)	1 (16.7)	2 (2.5)	1 (14.3)
Fatigue	3 (15.0)	1 (33.3)	2 (10.0)	0	6 (10.0)	0	8 (10.0)	0
Headache	3 (15.0)	0	4 (20.0)	0	8 (13.3)	0	12 (15.0)	0
Hepatic cirrhosis	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Injection site discolouration	1 (5.0)	0	1 (5.0)	0	7 (11.7)	0	8 (10.0)	0
Injection site erythema	1 (5.0)	0	2 (10.0)	0	11 (18.3)	0	13 (16.3)	0
Joint injury	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Lipoma	0	0	0	0	0	1 (16.7)	0	1 (14.3)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		Olezarsen 50 mg/ 80 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	< 65 Years (n = 20)	≥ 65 Years (n = 3)	< 65 Years (n = 20)	≥ 65 Years (n = 1)	< 65 Years (n = 60)	≥ 65 Years (n = 6)	< 65 Years (n = 80)	≥ 65 Years (n = 7)
Muscle spasms	0	0	0	0	1 (1.7)	1 (16.7)	1 (1.3)	1 (14.3)
Nasopharyngitis	1 (5.0)	0	4 (20.0)	0	4 (6.7)	0	8 (10.0)	0
Nausea	1 (5.0)	0	2 (10.0)	0	7 (11.7)	0	9 (11.3)	0
Onychomycosis	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Osteopenia	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Rhinorrhoea	0	0	1 (5.0)	0	0	1 (16.7)	1 (1.3)	1 (14.3)
Sinus arrhythmia	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Skin laceration	1 (5.0)	1 (33.3)	1 (5.0)	0	0	1 (16.7)	1 (1.3)	1 (14.3)
Sudden death	0	0	0	1 (100.0)	0	0	0	1 (14.3)
Trismus	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Urine albumin/creatinine ratio increased	0	0	1 (5.0)	0	1 (1.7)	1 (16.7)	2 (2.5)	1 (14.3)
Urine protein/creatinine ratio increased	0	0	1 (5.0)	0	2 (3.3)	1 (16.7)	3 (3.8)	1 (14.3)
Varices oesophageal	0	0	0	0	0	1 (16.7)	0	1 (14.3)
Vision blurred	1 (5.0)	0	0	0	1 (1.7)	1 (16.7)	1 (1.3)	1 (14.3)
Vomiting	0	0	1 (5.0)	0	7 (11.7)	0	8 (10.0)	0

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: The ISIS-678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS-678354 80 mg and then had their dose reduced to 50 mg

AEs by age range

The majority of patients in olezarsen clinical trials were younger than 65 years of age - 181 in olezarsen and 54 in placebo group. No patients of 85 or more years of age were randomized. Number of AEs in general was comparable in all 3 age groups. Postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures occurred more often in patients of 75-84 years of age – 17.4% vs. 5% in people < 65 years and 6.8% in people of 65-74 years. Number of serious AEs and nervous system disorders were more frequent in patients of 75-84 years of age: 17.4% vs. 14.4% (age <65) and 12.5% (age 65-74), and 21.7% vs. 17.7% (age <65) and 14.8% (age 65-74), respectively. To be noted however, that patient group of 75-84 years was the smallest one – 23 patients in olezarsen group, resulting in very small number of AEs in different areas, thus making comparison between age groups difficult. See the table below.

Table 83: AE summaries below for the pooled data from CS2, CS3, CS7, CS8, and CS13 (ISS Pool 5) (Source: ISS T2 and T3)

	Active				**Placebo**			
MedDRA Terms	**Age <65** N=181 **n (%)**	**Age 65-74** N=88 **n (%)**	**Age 75-84** N=23 **n (%)**	**Age 85+** N=0 **n (%)**	**Age <65** N=54 **n (%)**	**Age 65-74** N=23 **n (%)**	**Age 75-84** N=9 **n (%)**	**Age 85+** N=0 **n (%)**
Total AEs	148 (81.8)	77 (87.5)	18 (78.3)	0 (NA)	46 (85.2)	20 (87.0)	6 (66.7)	0 (NA)
Serious AEs – Total	26 (14.4)	11 (12.5)	4 (17.4)	0 (NA)	7 (13.0)	5 (21.7)	1 (11.1)	0 (NA)
- Fatal	1 (0.6)	1 (1.1)	1 (4.3)	0 (NA)	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)
- Hospitalization/prolong existing hospitalization	17 (9.4)	10 (11.4)	3 (13.0)	0 (NA)	7 (13.0)	4 (17.4)	0 (0.0)	0 (NA)
- Life-threatening	5 (2.8)	0 (0.0)	1 (4.3)	0 (NA)	2 (3.7)	0 (0.0)	0 (0.0)	0 (NA)
- Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)
- Other (medically significant)*	10 (5.5)	2 (2.3)	2 (8.7)	0 (NA)	3 (5.6)	2 (8.7)	1 (11.1)	0 (NA)
AE leading to drop-out	14 (7.7)	5 (5.7)	2 (8.7)	0 (NA)	0 (0.0)	1 (4.3)	0 (0.0)	0 (NA)
Psychiatric disorders	13 (7.2)	1 (1.1)	0 (0.0)	0 (NA)	4 (7.4)	4 (17.4)	1 (11.1)	0 (NA)
Nervous system disorders	32 (17.7)	13 (14.8)	5 (21.7)	0 (NA)	10 (18.5)	4 (17.4)	0 (0.0)	0 (NA)
Accidents and injuries	17 (9.4)	8 (9.1)	2 (8.7)	0 (NA)	6 (11.1)	7 (30.4)	1 (11.1)	0 (NA)
Cardiac disorders	12 (6.6)	8 (9.1)	2 (8.7)	0 (NA)	2 (3.7)	2 (8.7)	0 (0.0)	0 (NA)
Vascular disorders	15 (8.3)	8 (9.1)	2 (8.7)	0 (NA)	4 (7.4)	3 (13.0)	0 (0.0)	0 (NA)
Cerebrovascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)
Infections and infestations	79 (43.6)	45 (51.1)	10 (43.5)	0 (NA)	23 (42.6)	13 (56.5)	3 (33.3)	0 (NA)
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	9 (5.0)	6 (6.8)	4 (17.4)	0 (NA)	5 (9.3)	4 (17.4)	0 (0.0)	0 (NA)
<other AE appearing more frequently in older patients>	NA							

Patients took placebo in CS3 then took olezarsen in CS13 were included in both placebo and active treatment groups.

* Other medically significant events include SAEs classified as Congenital Anomaly and Important Medical Event

AE by special population

No hepatically impaired or pregnant patients were enrolled to olezarsen clinical trials. Limited number of renally impaired patients participated – 6 (3 of them experienced at least one AE) in olezarsen and 2 (they both experienced at least one AE each) in placebo group. No conclusions can be drawn or specific safety patterns detected in renally impaired patiernt population due to very limited number of such patients. See the table below for more details.

Table 84: AE by special population

	Active				**Placebo**			
MedDRA Terms	**Hepatically impaired*** **N=0** **n (%)**	**Renally impaired**** **N=6** **n (%)**	**Pregnant** **N=0** **n (%)**	**Other** **N=286** **n (%)**	**Hepatically impaired*** N=0 **n (%)**	**Renally impaired**** N=2 **n (%)**	**Pregnant** N=0 **n (%)**	**Other** N=84 **n (%)**
Total AEs	0 (NA)	3 (50.0)	0 (NA)	240 (83.9)	0 (NA)	2 (100.0)	0 (NA)	70 (83.3)
Serious AEs – Total	0 (NA)	1 (16.7)	0 (NA)	40 (14.0)	0 (NA)	0 (0.0)	0 (NA)	13 (15.5)
- Fatal	0 (NA)	0 (0.0)	0 (NA)	3 (1.0)	0 (NA)	0 (0.0)	0 (NA)	0 (0.0)
- Hospitalization/prolong existing hospitalization	0 (NA)	1 (16.7)	0 (NA)	29 (10.1)	0 (NA)	0 (0.0)	0 (NA)	11 (13.1)
- Life-threatening	0 (NA)	0 (0.0)	0 (NA)	6 (2.1)	0 (NA)	0 (0.0)	0 (NA)	2 (2.4)
- Disability/incapacity	0 (NA)	0 (0.0)	0 (NA)	0 (0.0)	0 (NA)	0 (0.0)	0 (NA)	0 (0.0)
- Other (medically significant) [1]	0 (NA)	1 (16.7)	0 (NA)	13 (4.5)	0 (NA)	0 (0.0)	0 (NA)	6 (7.1)
AE leading to drop-out	0 (NA)	0 (0.0)	0 (NA)	21 (7.3)	0 (NA)	0 (0.0)	0 (NA)	1 (1.2)

* Hepatic impairment, according to the NCI-ODWG criteria, is defined as moderate (total bilirubin >1.5–3 x ULN), with any AST level) or severe (total bilirubin >3–10 x ULN, with any AST level). This is equivalent to a Child-Pugh score of B or C.

** Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
Patients took placebo in CS3 then took olezarsen in CS13 were included in both placebo and active treatment groups.

[1] Other medically significant events include SAEs classified as Congenital Anomaly and Important Medical Event

Extrinsic Factors

Geographic Location

<u>US vs. Non-US</u>

Pool 1 (CS3 + CS8)

Table 85: Differences in Treatment-emergent Adverse Events by Geographic Location (US versus Non-US) by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		**Olezarsen 50 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	US (n = 42)	**Non-US (n = 20)**	**US (n = 60)**	**Non-US (n = 19)**	**US (n = 63)**	**Non-US (n = 16)**	**US (n = 123)**	**Non-US (n = 35)**
Patients with Any TEAE	32 (76.2)	20 (100.0)	43 (71.7)	18 (94.7)	43 (68.3)	14 (87.5)	86 (69.9)	32 (91.4)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	4 (9.5)	13 (65.0)	6 (10.0)	7 (36.8)	12 (19.0)	6 (37.5)	18 (14.6)	13 (37.1)
General disorders and administration site conditions	5 (11.9)	7 (35.0)	14 (23.3)	7 (36.8)	9 (14.3)	5 (31.3)	23 (18.7)	12 (34.3)
Infections and infestations	16 (38.1)	15 (75.0)	22 (36.7)	12 (63.2)	17 (27.0)	7 (43.8)	39 (31.7)	19 (54.3)
Musculoskeletal and connective tissue disorders	7 (16.7)	4 (20.0)	13 (21.7)	9 (47.4)	4 (6.3)	6 (37.5)	17 (13.8)	15 (42.9)
Nervous system disorders	5 (11.9)	6 (30.0)	3 (5.0)	9 (47.4)	7 (11.1)	2 (12.5)	10 (8.1)	11 (31.4)
Respiratory, thoracic and mediastinal disorders	4 (9.5)	5 (25.0)	7 (11.7)	6 (31.6)	6 (9.5)	4 (25.0)	13 (10.6)	10 (28.6)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	1 (2.4)	7 (35.0)	0	4 (21.1)	4 (6.3)	2 (12.5)	4 (3.3)	6 (17.1)
Arthralgia	2 (4.8)	0	3 (5.0)	5 (26.3)	0	1 (6.3)	3 (2.4)	6 (17.1)
Cough	2 (4.8)	2 (10.0)	1 (1.7)	2 (10.5)	2 (3.2)	3 (18.8)	3 (2.4)	5 (14.3)
COVID-19	3 (7.1)	7 (35.0)	7 (11.7)	4 (21.1)	3 (4.8)	4 (25.0)	10 (8.1)	8 (22.9)
Headache	1 (2.4)	3 (15.0)	0	5 (26.3)	2 (3.2)	1 (6.3)	2 (1.6)	6 (17.1)
Nausea	0	2 (10.0)	0	3 (15.8)	1 (1.6)	1 (6.3)	1 (0.8)	4 (11.4)
Platelet count decreased	0	1 (5.0)	0	1 (5.3)	1 (1.6)	3 (18.8)	1 (0.8)	4 (11.4)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Pool 4 (CS3 + CS7 + CS13)

Table 86: Differences in Treatment-emergent Adverse Events – Geographic Location (US versus Non-US) and Treatment Group by System Organ Class and Preferred Term (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		**Olezarsen 50 mg/80 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	US (n = 7)	**Non-US (n = 16)**	**US (n = 5)**	**Non-US (n = 16)**	**US (n = 16)**	**Non-US (n = 50)**	**US (n = 21)**	**Non-US (n = 66)**
Patients with Any TEAE	6 (85.7)	16 (100.0)	4 (80.0)	15 (93.8)	13 (81.3)	45 (90.0)	17 (81.0)	60 (90.9)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Infections and infestations	2 (28.6)	11 (68.8)	3 (60.0)	12 (75.0)	5 (31.3)	25 (50.0)	8 (38.1)	37 (56.1)
Metabolism and nutrition disorders	2 (28.6)	3 (18.8)	2 (40.0)	3 (18.8)	3 (18.8)	3 (6.0)	5 (23.8)	6 (9.1)
Psychiatric disorders	1 (14.3)	1 (6.3)	0	6 (37.5)	0	4 (8.0)	0	10 (15.2)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Influenza	0	2 (12.5)	1 (20.0)	5 (31.3)	0	6 (12.0)	1 (4.8)	11 (16.7)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		Olezarsen 50 mg/80 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	US (n = 7)	Non-US (n = 16)	US (n = 5)	Non-US (n = 16)	US (n = 16)	Non-US (n = 50)	US (n = 21)	Non-US (n = 66)
Injection site discolouration	0	1 (6.3)	0	1 (6.3)	0	7 (14.0)	0	8 (12.1)
Injection site erythema	0	1 (6.3)	1 (20.0)	1 (6.3)	4 (25.0)	7 (14.0)	5 (23.8)	8 (12.1)
Pain	0	0	1 (20.0)	0	2 (12.5)	1 (2.0)	3 (14.3)	1 (1.5)
Vomiting	0	0	0	1 (6.3)	0	7 (14.0)	0	8 (12.1)

Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: For the summarization of number of patients (n), a patient was counted only once even if > 1 event was reported.
Note: The analysis set was used in conjunction with the analysis period and treatment group to uniquely identify the patients and data contributing to the analyses. For patients who received placebo in CS3 and rolled over to CS13, their data from the date and time of first dose in CS3 up to (but not including) the date and time of first dose in CS13 were included in the placebo group; their data from the date and time of first dose in CS13 were included in the olezarsen group.
Note: The ISIS-678354 50 mg/80 mg group includes patients who were randomized to and received 50 mg in CS3, regardless of whether they rolled over to CS13. This group does not include patients who were initially randomized to ISIS-678354 80 mg and then had their dose reduced to 50 mg

North America vs Europe

Pool 1 (CS3 + CS8)

Table 87: Differences in Treatment-emergent Adverse Events by Geographic Location (North America versus Europe) by System Organ Class and Preferred Term (Pool 1)

	Pool 1 Study CS3 + Study CS8							
	Placebo n (%)		Olezarsen 50 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	North America (n = 51)	Europe (n = 11)	North America (n = 67)	Europe (n = 12)	North America (n = 65)	Europe (n = 14)	North America (n = 132)	Europe (n = 26)
Patients with Any TEAE	41 (80.4)	11 (100.0)	50 (74.6)	11 (91.7)	45 (69.2)	12 (85.7)	95 (72.0)	23 (88.5)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	8 (15.7)	9 (81.8)	7 (10.4)	6 (50.0)	13 (20.0)	5 (35.7)	20 (15.2)	11 (42.3)
General disorders and administration site conditions	9 (17.6)	3 (27.3)	17 (25.4)	4 (33.3)	10 (15.4)	4 (28.6)	27 (20.5)	8 (30.8)
Infections and infestations	24 (47.1)	7 (63.6)	27 (40.3)	7 (58.3)	18 (27.7)	6 (42.9)	45 (34.1)	13 (50.0)
Injury, poisoning and procedural complications	9 (17.6)	0	5 (7.5)	4 (33.3)	5 (7.7)	1 (7.1)	10 (7.6)	5 (19.2)
Metabolism and nutrition disorders	11 (21.6)	1 (9.1)	9 (13.4)	1 (8.3)	10 (15.4)	0	19 (14.4)	1 (3.8)
Musculoskeletal and connective tissue disorders	9 (17.6)	2 (18.2)	18 (26.9)	4 (33.3)	5 (7.7)	5 (35.7)	23 (17.4)	9 (34.6)
Nervous system disorders	7 (13.7)	4 (36.4)	8 (11.9)	4 (33.3)	7 (10.8)	2 (14.3)	15 (11.4)	6 (23.1)
Reproductive system and breast disorders	1 (2.0)	0	1 (1.5)	2 (16.7)	1 (1.5)	1 (7.1)	2 (1.5)	3 (11.5)
Respiratory, thoracic and mediastinal disorders	6 (11.8)	3 (27.3)	9 (13.4)	4 (33.3)	7 (10.8)	3 (21.4)	16 (12.1)	7 (26.9)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	3 (5.9)	5 (45.5)	1 (1.5)	3 (25.0)	4 (6.2)	2 (14.3)	5 (3.8)	5 (19.2)
Headache	3 (5.9)	1 (9.1)	2 (3.0)	3 (25.0)	2 (3.1)	1 (7.1)	4 (3.0)	4 (15.4)
Nausea	2 (3.9)	0	1 (1.5)	2 (16.7)	1 (1.5)	1 (7.1)	2 (1.5)	3 (11.5)
Platelet count decreased	0	1 (9.1)	0	1 (8.3)	1 (1.5)	3 (21.4)	1 (0.8)	4 (15.4)
Vomiting	0	0	0	1 (8.3)	0	2 (14.3)	0	3 (11.5)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Pool 4 (CS3 + CS7 + CS13)

Table 88: Differences in Treatment-emergent Adverse Events by Geographic Location (North America versus Europe) by System Organ Class and Preferred Term (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		**Olezarsen 50 mg/80 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	North America (n = 12)	**Europe (n = 11)**	**North America (n = 9)**	**Europe (n = 12)**	**North America (n = 40)**	**Europe (n = 26)**	**North America (n = 49)**	**Europe (n = 38)**
Patients with Any TEAE	11 (91.7)	11 (100.0)	8 (88.9)	11 (91.7)	37 (92.5)	21 (80.8)	45 (91.8)	32 (84.2)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Gastrointestinal disorders	7 (58.3)	9 (81.8)	1 (11.1)	6 (50.0)	24 (60.0)	9 (34.6)	25 (51.0)	15 (39.5)
General disorders and administration site conditions	5 (41.7)	3 (27.3)	4 (44.4)	4 (33.3)	20 (50.0)	10 (38.5)	24 (49.0)	14 (36.8)
Infections and infestations	6 (50.0)	7 (63.6)	7 (77.8)	8 (66.7)	21 (52.5)	9 (34.6)	28 (57.1)	17 (44.7)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	3 (25.0)	5 (45.5)	0	3 (25.0)	13 (32.5)	2 (7.7)	13 (26.5)	5 (13.2)
COVID-19	4 (33.3)	4 (36.4)	7 (77.8)	3 (25.0)	9 (22.5)	4 (15.4)	16 (32.7)	7 (18.4)
Fatigue	4 (33.3)	0	2 (22.2)	0	6 (15.0)	0	8 (16.3)	0
Injection site erythema	0	1 (9.1)	2 (22.2)	0	10 (25.0)	1 (3.8)	12 (24.5)	1 (2.6)
Myalgia	0	0	0	0	6 (15.0)	0	6 (12.2)	0
Oropharyngeal pain	0	0	0	1 (8.3)	8 (20.0)	0	8 (16.3)	1 (2.6)
Platelet count decreased	0	1 (9.1)	0	1 (8.3)	0	3 (11.5)	0	4 (10.5)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

Previous Treatment with Volanesorsen

Patients treated previously with volanesorsen were only enrolled in Studies CS3, CS13 and CS7; no patients enrolled in Studies CS2 and CS8 were previously treated with volanesorsen. Therefore, Pool 4 (CS3 + CS13 + CS7) provides the most appropriate evaluation of safety by prior use of volanesorsen and is described below.

Table 89: Differences in Treatment-emergent Adverse Events by Prior Treatment with Volanesorsen by System Organ Class and Preferred Term (Pool 4)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		**Olezarsen 50 mg/80 mg n (%)**		**Olezarsen 80 mg n (%)**		**Total Olezarsen n (%)**	
	Prior Volanesorsen (n = 10)	**No Prior Volanesorsen (n = 13)**	**Prior Volanesorsen (n = 8)**	**No Prior Volanesorsen (n = 13)**	**Prior Volanesorsen (n = 41)**	**No Prior Volanesorsen (n = 25)**	**Prior Volanesorsen (n = 49)**	**No Prior Volanesorsen (n = 38)**
Patients with Any TEAE	10 (100.0)	12 (92.3)	8 (100.0)	11 (84.6)	38 (92.7)	20 (80.0)	46 (93.9)	31 (81.6)
System Organ Classes with ≥ 10% Difference Between Subgroups								
Eye disorders	1 (10.0)	1 (7.7)	1 (12.5)	0	4 (9.8)	0	5 (10.2)	0
Gastrointestinal disorders	7 (70.0)	9 (69.2)	4 (50.0)	3 (23.1)	24 (58.5)	9 (36.0)	28 (57.1)	12 (31.6)

	Pool 4 Study CS3 + Study CS7 + Study CS13							
	Placebo n (%)		Olezarsen 50 mg/80 mg n (%)		Olezarsen 80 mg n (%)		Total Olezarsen n (%)	
	Prior Volanesorsen (n = 10)	No Prior Volanesorsen (n = 13)	Prior Volanesorsen (n = 8)	No Prior Volanesorsen (n = 13)	Prior Volanesorsen (n = 41)	No Prior Volanesorsen (n = 25)	Prior Volanesorsen (n = 49)	No Prior Volanesorsen (n = 38)
Infections and infestations	6 (60.0)	7 (53.8)	6 (75.0)	9 (69.2)	22 (53.7)	8 (32.0)	28 (57.1)	17 (44.7)
Preferred Terms with ≥ 10% Difference Between Subgroups								
Abdominal pain	3 (30.0)	5 (38.5)	2 (25.0)	1 (7.7)	12 (29.3)	3 (12.0)	14 (28.6)	4 (10.5)
Chills	0	0	1 (12.5)	0	5 (12.2)	0	6 (12.2)	0
Diarrhoea	2 (20.0)	4 (30.8)	1 (12.5)	0	5 (12.2)	0	6 (12.2)	0
Myalgia	0	0	0	0	6 (14.6)	0	6 (12.2)	0
Nasopharyngitis	1 (10.0)	0	3 (37.5)	1 (7.7)	4 (9.8)	0	7 (14.3)	1 (2.6)
Vomiting	0	0	1 (12.5)	0	6 (14.6)	1 (4.0)	7 (14.3)	1 (2.6)

Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.

2.5.8.7. Immunological events

Study CS3

There does not appear to be any association of ADA status (negative, treatment-unaffected, or treatment-emergent) with the frequency of TEAEs, their severity, or their relationship to treatment, nor were there any such associations for serious TEAEs. In terms of individual AEs, there were no obvious general relationships between TEAEs and ADA status.

No patient in any treatment group experienced an AESI during study CS3.

With respect to ISR OAEIs, of the 8 patients who experienced ISRs (i.e., 3 each in olezarsen 80 mg group and olezarsen 50 mg group; 2 in placebo group), 3 patients (1 in olezarsen 80 mg group; 2 in olezarsen 50 mg group) had treatment-emergent ADAs, 4 patients (1 each in olezarsen 80 mg group and olezarsen 50 mg group; 2 in placebo group, respectively) had treatment-unaffected ADAs, and 1 patient (in olezarsen 80 mg group) was ADA negative. From these data, there was no obvious relationship between ISRs and ADA status, though small sample sizes limit interpretation of the data.

With respect to flu-like reaction OAEIs, patients that experienced flu-like reactions in the olezarsen 50 mg group and olezarsen 80 mg group (i.e., 1 patient each) both had treatment-unaffected ADAs. The limited number of these TEAEs limits interpretation of this data.

With respect to hypersensitivity OAEIs, of the 5 patients who experienced hypersensitivity TEAEs per Hypersensitivity FMQ (broad) (i.e., 2 each in the olezarsen 80 mg group and olezarsen 50 mg group; 1 in the placebo group), 1 patient (in the olezarsen 50 mg group) had treatment-emergent ADA, 1 patient (in the olezarsen 50 mg group) had treatment-unaffected ADA, and 3 (2 in the olezarsen 80 mg group, 1 in the placebo group) patients were ADA negative, including the patient in the olezarsen 80 mg group who permanently discontinued study drug due to the potential hypersensitivity TEAE of flushing (moderate). Based on these data, there was no correlative relationship between hypersensitivity reactions and ADA status, though small sample sizes limit interpretation of the data.

Two patients (1 patient in the olezarsen 80 mg group and 1 patient in the olezarsen 50 mg group) exhibited a peak ADA titer of 25,600 (> 100-fold higher than median peak ADA titer of 75 and 200 for the 50 mg and 80 mg olezarsen treatment groups, respectively):

- One patient, a 62-year-old female patient, in the olezarsen 80 mg treatment group, had an ADA titer of 3200 on Study Day 1. The patient was treated with volanesorsen prior to Study CS3. The patient had a peak ADA titer of 25,600 on Study Days 184 and 366. The patient did not experience any TEAEs at the time of the peak ADA titer and did not experience any ISR, flu-like reaction, hypersensitivity reactions, or any related serious or severe events during the study. The patient completed treatment and rolled over to the open-label study CS13.
- One patient, a 74-year-old female patient, in the olezarsen 50 mg treatment group, had an ADA titer of 1600 on Study Day 1. The patient was treated with volanesorsen prior to Study CS3. The patient had a peak ADA titer of 25,600 on Study Days 15 and 30. The patient's last treatment with study drug was on Study Day 30. The patient did not experience any TEAEs at the time of the peak ADA titer. On Study Day 42, the patient died suddenly (sudden death). Cause of death was unknown. The fatality was considered unlikely related to study drug by the Investigator and Sponsor.

Safety profiles were generally similar between ADA-positive and ADA-negative patients, and there was no clinically meaningful impact of ADA status on safety profiles.

Pool 1 (CS3 + CS8)

Among 79 patients in the olezarsen 80 mg group, 79 patients in the olezarsen 50 mg group and 62 patients in the placebo group, 42 (53.2%), 40 (50.6%), and 20 (32.3%) patients had a positive ADA status, respectively; including 33 (41.8%), 32 (40.5%), and 5 (8.1%) patients who had a treatment-emergent antibody status, respectively; and 9 (11.4%), 8 (10.1%), and 15 (24.2%) patients who had a treatment-unaffected antibody status, respectively. At Baseline, 17 (21.5%), 17 (21.5%), and 19 (30.6%) patients were ADA positive, respectively.

The median (range) peak ADA titers in patient with treatment-emergent ADA were 100 (50, 51200), 200 (50, 25600), and 100 (50, 1600) in the olezarsen 80 mg group, olezarsen 50 mg group and the placebo group, respectively; median time to reach peak titer was 92.0 days, 85.0 days, and 169.0 days, respectively.

With respect to serious TEAEs, 11 patients in the olezarsen 80 mg group experienced a serious TEAE, including 6 (18.2%) of 33 patients with treatment-emergent ADAs, 0 of 9 patients with treatment-unaffected ADAs, and 5 (13.5%) of 37 ADA-negative patients. Ten patients in the olezarsen 50 mg group experienced a serious TEAE, including 5 (15.6%) of 32 patients with treatment-emergent ADAs, 1 (12.5%) of 8 patients with treatment-unaffected ADAs, and 4 (10.3%) of 39 ADA-negative patients. Eleven patients in the placebo group experienced a serious TEAE, including 0 of 5 patients with treatment-emergent ADAs, 6 (40.0%) of 15 patients with treatment-unaffected ADAs, and 5 (11.9%) of 42 ADA-negative patients.

With respect to severe TEAEs, 4 patients in the olezarsen 80 mg group experienced at least 1 severe TEAEs, including 1 (3.0%) of 33 patients with treatment-emergent ADAs, 0 of 9 patients with treatment-unaffected ADAs, and 3 (8.1%) of 37 ADA-negative patients. Six patients in the olezarsen 50 mg group experienced at least 1 severe TEAE, including 4 (12.5%) of 32 patients with treatment-emergent ADAs, 1 (12.5%) of 8 patients with treatment-unaffected ADAs, and 1 (2.6%) of 39 ADA-negative patients. Ten patients in the placebo group experienced at least 1 severe TEAE, including 0 of 5 patients with treatment-emergent ADAs, 4 (26.7%) of 15 patients with treatment-unaffected ADAs, and 6 (14.3%) of 42 ADA-negative patients.

No patient in any treatment group experienced an AESI in Pool 1.

With respect to bleeding OAEIs, of the 19 patients who experienced bleeding TEAEs (i.e., 7 patients in the olezarsen 80 mg group, 6 patients in the olezarsen 50 mg group, and 6 patients in the placebo

group); 6 patients (5 patients in the olezarsen 80 mg group and 1 patient in the olezarsen 50 mg group) had treatment-emergent ADA, 5 patients (1 patient in the olezarsen 80 mg group and 4 patients in the placebo group) had treatment-unaffected ADA, and 8 patients (1 patient in the olezarsen 80 mg group, 5 patients in the olezarsen 50 mg group, and 2 patients in the placebo group) were ADA negative.

With respect to thrombocytopenia OAEIs, of the 8 patients who experienced thrombocytopenia TEAEs (i.e., 4 patients in the olezarsen 80 mg group, 1 patient in the olezarsen 50 mg group, and 1 patient in the placebo group), 1 patient (olezarsen 80 mg group) had treatment-emergent ADA, 1 patient (olezarsen 50 mg group) had treatment-unaffected ADA, and 6 patients (4 patients in the olezarsen 80 mg group, 1 patient in the olezarsen 50 mg group, and 1 patient in the placebo group) were ADA negative.

With respect to ISR OAEIs, of the 21 patients who experienced an injection site TEAE (i.e., 6 patients in the olezarsen 80 mg group, 13 patients in the olezarsen 50 mg group, and 2 patients in the placebo group); 8 patients (2 patients in the olezarsen 80 mg group and 6 patients in the olezarsen 50 mg group) had treatment-emergent ADA, 5 patients (2 patients in the olezarsen 80 mg group, 1 patient in the olezarsen 50 mg group, and 2 patients in the placebo group) had treatment-unaffected ADA, and 8 patients (2 patients in the olezarsen 80 mg group, and 6 patients in the olezarsen 50 mg group) were ADA negative.

With respect to flu-like reaction (FLR 1) OAEIs, both patients that experienced flu-like reactions in the olezarsen 50 mg group and olezarsen 80 mg group (i.e., 1 patient each) had treatment-unaffected ADAs. The limited number of these TEAEs limits interpretation of this data.

With respect to hypersensitivity OAEIs, of the 11 patients who experienced hypersensitivity TEAEs per Hypersensitivity FMQ (broad) (i.e., 3 patients in the olezarsen 80 mg group, 7 patients in the olezarsen 50 mg group, and 1 patient in the placebo group), 3 patients (in the olezarsen 50 mg group) had treatment-emergent ADA, 2 patients (1 patient in the olezarsen 80 mg group and 1 patient in the olezarsen 50 mg group) had treatment-unaffected ADA, and 6 patients (2 patients in the olezarsen 80 mg group, 3 patients in the olezarsen 50 mg group, and 1 patient in the placebo group) were ADA negative.

With respect to renal function OAEIs, of the 5 patients who experienced TEAEs per Acute Kidney Injury FMQ (broad) (i.e., 1 patient in the olezarsen 80 mg group, 1 patient in the olezarsen 50 mg group, and 3 patients in the placebo group), all patients were ADA negative.

With respect to abnormal liver function OAEIs, of the 12 patients who experienced TEAEs per Hepatic Injury and Hepatic Failure FMQ (Narrow) (i.e., 5 patients in the olezarsen 80 mg group, 4 patients in the olezarsen 50 mg group, and 3 patients in the placebo group), 2 patients (1 patient each in the olezarsen 80 mg group and olezarsen 50 mg group) had treatment-emergent ADA, 3 patients (1 patient in the olezarsen 50 mg group and 2 patients in the placebo group) had treatment-unaffected ADA, and 7 patients (4 patients in the olezarsen 80 mg group, 2 patients in the olezarsen 50 mg group, and 1 patient in the placebo group) were ADA negative.

A total of 3 patients in Pool 1 exhibited a peak ADA titer that was > 100-fold higher than median peak ADA titer. There were 2 patients in Study CS3 (1 patient in the olezarsen 80 mg group and 1 patient in the olezarsen 50 mg group) who exhibited a peak ADA titer of 25,600 (see Section 6.1), and 1 patient in Study CS8 (olezarsen 80 mg group) who exhibited a peak ADA titer of 51,200 (see Section 6.2).

In Pool 1, there does not appear to be a clear association between ADA status and the frequency of TEAEs, their severity, relationship to treatment, or seriousness. In addition, there does not appear to be meaningful differences in the incidence rate of individual TEAEs and OAEIs between patients by ADA

status and across peak ADA titer quartile groups. However, small sample sizes limit interpretation of the data.

Pool 4 (CS3 + CS13 + CS7)

Among 66 patients in the olezarsen 80 mg group, 21 patients in the olezarsen 50 mg/80 mg group, and 23 patients in the placebo group, 41 (62.1%), 14 (66.7%), and 9 (39.1%) patients had a positive ADA status, respectively; including 33 (50.0%), 11 (52.4%), and no patients who had a treatment-emergent antibody status, respectively; and 8 (12.1%), 3 (14.3%), and 9 (39.1%) patients who had a treatment-unaffected antibody status, respectively. At Baseline, 20 (30.3%), 8 (38.1%), and 10 (43.5%) patients were ADA positive, respectively.

The median (range) peak ADA titers in patients with treatment-emergent ADA were 200 (50, 25600) and 400 (50, 25600) in the olezarsen 80 mg group and the olezarsen 50 mg/80 mg group, respectively; median time to reach peak titer was 260.0 days and 397.0 days, respectively. No patients had a treatment-emergent antibody status in the placebo group.

With respect to serious TEAEs, 11 patients in the olezarsen 80 mg group experienced a serious TEAE, including 8 (24.2%) of 33 patients with treatment-emergent ADAs, 1 (12.5%) of 8 patients with treatment-unaffected ADAs, and 2 (8.0%) of 25 ADA-negative patients. Five patients in the olezarsen 50 mg/80 mg group experienced a serious TEAE, including 3 (27.3%) of 11 patients with treatment-emergent ADAs, 1 (33.3%) of 3 patients with treatment-unaffected ADAs, and 1 (14.3%) of 7 ADA-negative patients. Nine patients in placebo group experienced a serious TEAE, including 0 of 0 patients with treatment-emergent ADAs, 6 (66.7%) of 9 patients with treatment-unaffected ADAs, and 3 (21.4%) of 14 ADA-negative patients.

With respect to severe TEAEs, 5 patients in the olezarsen 80 mg group experienced at least 1 severe TEAE, including 3 (9.1%) of 33 patients with treatment-emergent ADAs, 1 (12.5%) of 8 patients with treatment-unaffected ADAs, and 1 (4.0%) of 25 ADA-negative patients. Three patients in the olezarsen 50 mg/80 mg group experienced at least 1 severe TEAE, including 2 (18.2%) of 11 patients with treatment-emergent ADAs, 1 (33.3%) of 3 patients with treatment-unaffected ADAs, and 0 of 7 ADA-negative patients. Nine patients in placebo group experienced at least 1 severe TEAE, including 0 of 0 patients with treatment-emergent ADAs, 4 (44.4%) of 9 patients with treatment-unaffected ADAs, and 5 (35.7%) of 14 ADA-negative patients.

One AESI occurred in Pool 4 in a Study CS13 patient with treatment-emergent ADAs.

With respect to bleeding OAEIs, of the 15 patients who experienced bleeding TEAEs (i.e., 8 patients in the olezarsen 80 mg group, 3 patients in the olezarsen 50 mg/80 mg group, and 4 patients in the placebo group), 5 patients (olezarsen 80 mg group) had treatment-emergent ADA, 4 patients (1 patient in the olezarsen 80 mg group and 3 patients in the placebo group) had treatment-unaffected ADA, and 6 patients (2 patients in the olezarsen 80 mg group, 3 patients in the olezarsen 50 mg/80 mg group, and 1 patient in the placebo group) were ADA negative.

With respect to thrombocytopenia OAEIs, of the 6 patients who experienced a thrombocytopenia TEAEs (i.e., 3 patients in the olezarsen 80 mg group, 2 patients in the olezarsen 50 mg/80 mg group, and 1 patient in the placebo group), 2 patients (olezarsen 80 mg group) had treatment-emergent ADA, 1 patient (olezarsen 50 mg/80 mg group) had treatment-unaffected ADA, and 3 patients (1 patient in each treatment group) were ADA negative.

With respect to ISR OAEIs, of the 17 patients who experienced an injection site TEAE (i.e., 11 patients in the olezarsen 80 mg group, 4 patients in the olezarsen 50 mg/80 mg group, and 2 patients in the placebo group), 12 patients (8 patients in the olezarsen 80 mg group and 4 patients in the olezarsen 50 mg/80 mg group) had treatment-emergent ADA, 3 patients (1 patient in the olezarsen 80 mg group, and 2 patients in the placebo group) had treatment-unaffected ADA, and 2 patients (olezarsen 80 mg group) were ADA negative.

With respect to flu-like reaction OAEIs per FLR 1, of the 8 patients who experienced flu like reactions (i.e., 7 patients in the olezarsen 80 mg group, and 1 patient in the olezarsen 50 mg/80 mg group), 6 patients (5 patients in the olezarsen 80 mg group, and 1 patient in the olezarsen 50 mg/80 mg) had treatment-emergent ADA, and 2 patients (olezarsen 80 mg group) had treatment-unaffected ADA. No patients were ADA negative. No patients in the placebo group experienced flu-like reactions.

With respect to hypersensitivity OAEIs, of the 13 patients who experienced hypersensitivity TEAEs per Hypersensitivity FMQ (broad) (i.e., 9 patients in the olezarsen 80 mg group, 3 patients in the olezarsen 50 mg/80 mg group, and 1 patient in the placebo group), 8 patients (5 patients in the olezarsen 80 mg group and 3 patients in the olezarsen 50 mg/80 mg group) had treatment-emergent ADA, no patients had treatment-unaffected ADA, and 5 patients (4 patients in the olezarsen 80 mg group, and 1 patient in the placebo group) were ADA negative. Serious hypersensitivity events were observed in 3 patients shortly after olezarsen administration and resulted in permanent discontinuation of olezarsen (peak ADA titers were 25,600 in 2 patients and 6400 in 1 patient).

With respect to renal function OAEIs, of the 2 patients who experienced TEAEs per Acute Kidney Injury FMQ (broad), 1 patient (olezarsen 80 mg) had treatment-emergent ADA and 1 patient (olezarsen 80 mg) was ADA negative. No patients had treatment-unaffected ADA. Patients in the olezarsen 50 mg/80 mg group and patients in the placebo group did not experience any TEAEs per Acute Kidney Injury FMQ (broad) criteria.

With respect to abnormal liver function OAEIs, of the 5 patients who experienced TEAEs per Hepatic Injury and Hepatic Failure FMQ (Narrow) (i.e., 3 patients in the olezarsen 80 mg group, and 2 patients in the placebo group), 2 patients (olezarsen 80 mg group) had treatment-emergent ADA, 1 patient (placebo group) had treatment-unaffected ADA, and 2 patients (1 patient in the olezarsen 80 mg group, and 1 patient in the placebo group) were ADA negative.

A total of 4 patients in Pool 4 exhibited a high peak ADA titer (> 100 fold higher than median peak ADA titer). One patient exhibited a peak ADA titer of 25,600 in both CS3 and CS13, so it is only counted once. There were 2 patients in Study CS3 (1 patient in the olezarsen 80 mg group and 1 patient in the olezarsen 50 mg/80 mg group) and 3 patients in Study CS13 (olezarsen 80 mg) who exhibited a peak ADA titer of 25,600.

In Pool 4, there does not appear to be a clear association between ADA status and the frequency of TEAEs, their severity, relationship to treatment, and seriousness. In addition, there does not appear to be differences in the incidence rate of these TEAEs and between patients by ADA status across peak ADA titer quartile groups, with the exception of the ISR and FLR 1 OAEIs. However, small sample sizes limit interpretation of a meaningful association of the data.

An overview of TEAEs in Pool 1 and Pool 4 by patient ADA Category and by peak ADA titer quartile is provided in tables below.

Table 90: Overview of Treatment-Emergent Adverse Events by Patient ADA Category (Pool 1 and Pool 4)

	ADA Category	Pool 1 Study CS3 + Study CS8				Pool 4 Study CS3 + Study CS7 + Study CS13			
			Olezarsen				Olezarsen		
	Neg TU TE	Placebo (N = 42) (N = 15) (N = 5) n (%)	50 mg (N = 39) (N = 8) (N = 32) n (%)	80 mg (N = 37) (N = 9) (N = 33) n (%)	Total Olezarsen (N = 76) (N = 17) (N = 65) n (%)	Placebo (N = 14) (N = 9) (N = 0) n (%)	50 mg/ 80 mg (N = 7) (N = 3) (N = 11) n (%)	80 mg (N = 25) (N = 8) (N = 33) n (%)	Total Olezarsen (N = 32) (N = 11) (N = 44) n (%)
Patients with At Least One TEAE	Neg	35 (83.3)	33 (84.6)	29 (78.4)	62 (81.6)	13 (92.9)	7 (100.0)	21 (84.0)	28 (87.5)
	TU	14 (93.3)	5 (62.5)	6 (66.7)	11 (64.7)	9 (100.0)	2 (66.7)	6 (75.0)	8 (72.7)
	TE	3 (60.0)	23 (71.9)	22 (66.7)	45 (69.2)	0	10 (90.9)	31 (93.9)	41 (93.2)
Patients with At Least One Serious TEAE	Neg	5 (11.9)	4 (10.3)	5 (13.5)	9 (11.8)	3 (21.4)	1 (14.3)	2 (8.0)	3 (9.4)
	TU	6 (40.0)	1 (12.5)	0	1 (5.9)	6 (66.7)	1 (33.3)	1 (12.5)	2 (18.2)
	TE	0	5 (15.6)	6 (18.2)	11 (16.9)	0	3 (27.3)	8 (24.2)	11 (25.0)
Patients with At Least One TEAE Related to Study Drug	Neg	6 (14.3)	11 (28.2)	9 (24.3)	20 (26.3)	3 (21.4)	2 (28.6)	10 (40.0)	12 (37.5)
	TU	2 (13.3)	4 (50.0)	3 (33.3)	7 (41.2)	2 (22.2)	1 (33.3)	4 (50.0)	5 (45.5)
	TE	0	7 (21.9)	3 (9.1)	10 (15.4)	0	5 (45.5)	17 (51.5)	22 (50.0)
Patients with At Least One Serious TEAE Related to Study Drug	Neg	0	0	0	0	0	0	1 (4.0)	1 (3.1)
	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	2 (6.1)	2 (4.5)
Patients with At Least One TEAE by Maximum Severity									
Mild	Neg	13 (31.0)	16 (41.0)	14 (37.8)	30 (39.5)	5 (35.7)	3 (42.9)	12 (48.0)	15 (46.9)
	TU	6 (40.0)	0 (0.0)	3 (33.3)	3 (17.6)	2 (22.2)	1 (33.3)	4 (50.0)	5 (45.5)
	TE	2 (40.0)	11 (34.4)	13 (39.4)	24 (36.9)	0	4 (36.4)	11 (33.3)	15 (34.1)
Moderate	Neg	16 (38.1)	16 (41.0)	12 (32.4)	28 (36.8)	3 (21.4)	4 (57.1)	8 (32.0)	12 (37.5)
	TU	4 (26.7)	4 (50.0)	3 (33.3)	7 (41.2)	3 (33.3)	0 (0.0)	1 (12.5)	1 (9.1)
	TE	1 (20.0)	8 (25.0)	8 (24.2)	16 (24.6)	0	4 (36.4)	17 (51.5)	21 (47.7)
Severe	Neg	6 (14.3)	1 (2.6)	3 (8.1)	4 (5.3)	5 (35.7)	0	1 (4.0)	1 (3.1)
	TU	4 (26.7)	1 (12.5)	0	1 (5.9)	4 (44.4)	1 (33.3)	1 (12.5)	2 (18.2)
	TE	0	4 (12.5)	1 (3.0)	5 (7.7)	0	2 (18.2)	3 (9.1)	5 (11.4)
Patients with At Least One TEAE Related to Study Drug by Maximum Severity									
Mild	Neg	5 (11.9)	11 (28.2)	6 (16.2)	17 (22.4)	2 (14.3)	2 (28.6)	6 (24.0)	8 (25.0)

	ADA Category	Pool 1 Study CS3 + Study CS8				Pool 4 Study CS3 + Study CS7 + Study CS13			
			Olezarsen				Olezarsen		
	Neg TU TE	Placebo (N = 42) (N = 15) (N = 5) n (%)	50 mg (N = 39) (N = 8) (N = 32) n (%)	80 mg (N = 37) (N = 9) (N = 33) n (%)	Total Olezarsen (N = 76) (N = 17) (N = 65) n (%)	Placebo (N = 14) (N = 9) (N = 0) n (%)	50 mg/ 80 mg (N = 7) (N = 3) (N = 11) n (%)	80 mg (N = 25) (N = 8) (N = 33) n (%)	Total Olezarsen (N = 32) (N = 11) (N = 44) n (%)
	TU	1 (6.7)	4 (50.0)	2 (22.2)	6 (35.3)	1 (11.1)	1 (33.3)	3 (37.5)	4 (36.4)
	TE	0	5 (15.6)	2 (6.1)	7 (10.8)	0	3 (27.3)	11 (33.3)	14 (31.8)
Moderate	Neg	0	0	3 (8.1)	3 (3.9)	0	0	4 (16.0)	4 (12.5)
	TU	0	0	1 (11.1)	1 (5.9)	0	0	1 (12.5)	1 (9.1)
	TE	0	2 (6.3)	1 (3.0)	3 (4.6)	0	2 (18.2)	4 (12.1)	6 (13.6)
Severe	Neg	1 (2.4)	0	0	0	1 (7.1)	0	0	0
	TU	1 (6.7)	0	0	0	1 (11.1)	0	0	0
	TE	0	0	0	0	0	0	2 (6.1)	2 (4.5)
Patients with At Least One TEAE Leading to Treatment Discontinuation	Neg	0	4 (10.3)	3 (8.1)	7 (9.2)	0	0	2 (8.0)	2 (6.3)
	TU	0	0	2 (22.2)	2 (11.8)	0	0	1 (12.5)	1 (9.1)
	TE	0	5 (15.6)	0	5 (7.7)	0	1 (9.1)	4 (12.1)	5 (11.4)
Patients with At Least One TEAE Related to Study Drug Leading to Treatment Discontinuation	Neg	0	1 (2.6)	2 (5.4)	3 (3.9)	0	0	2 (8.0)	2 (6.3)
	TU	0	0	2 (22.2)	2 (11.8)	0	0	1 (12.5)	1 (9.1)
	TE	0	2 (6.3)	0	2 (3.1)	0	0	3 (9.1)	3 (6.8)
Patients with At Least One TEAE Leading to Death	Neg	0	0	0	0	0	0	0	0
	TU	0	0	0	0	0	0	0	0
	TE	0	2 (6.3)	0	2 (3.1)	0	1 (9.1)	0	1 (2.3)
Patients with At Least One Bleeding TEAE	Neg	2 (4.8)	5 (12.8)	1 (2.7)	6 (7.9)	1 (7.1)	3 (42.9)	2 (8.0)	5 (15.6)
	TU	4 (26.7)	0	1 (11.1)	1 (5.9)	3 (33.3)	0	1 (12.5)	1 (9.1)
	TE	0	1 (3.1)	5 (15.2)	6 (9.2)	0	0	5 (15.2)	5 (11.4)
Patients with At Least One Thrombocytopenia TEAE	Neg	1 (2.4)	1 (2.6)	4 (10.8)	5 (6.6)	1 (7.1)	1 (14.3)	1 (4.0)	2 (6.3)
	TU	0	1 (12.5)	0	1 (5.9)	0	1 (33.3)	0	1 (9.1)
	TE	0	0	1 (3.0)	1 (1.5)	0	0	2 (6.1)	2 (4.5)
Patients with At Least One Hypersensitivity TEAE (FMQ Narrow)	Neg	0	0	0	0	0	0	1 (4.0)	1 (3.1)
	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	2 (6.1)	2 (4.5)

	ADA Category	Pool 1 Study CS3 + Study CS8				Pool 4 Study CS3 + Study CS7 + Study CS13			
			Olezarsen				Olezarsen		
	Neg TU TE	Placebo (N = 42) (N = 15) (N = 5) n (%)	50 mg (N = 39) (N = 8) (N = 32) n (%)	80 mg (N = 37) (N = 9) (N = 33) n (%)	Total Olezarsen (N = 76) (N = 17) (N = 65) n (%)	Placebo (N = 14) (N = 9) (N = 0) n (%)	50 mg/ 80 mg (N = 7) (N = 3) (N = 11) n (%)	80 mg (N = 25) (N = 8) (N = 33) n (%)	Total Olezarsen (N = 32) (N = 11) (N = 44) n (%)
Patients with At Least One Hypersensitivity TEAE (FMQ Broad)	Neg	1 (2.4)	3 (7.7)	2 (5.4)	5 (6.6)	1 (7.1)	0	4 (16.0)	4 (12.5)
	TU	0	1 (12.5)	1 (11.1)	2 (11.8)	0	0	0	0
	TE	0	3 (9.4)	0	3 (4.6)	0	3 (27.3)	5 (15.2)	8 (18.2)
Patients with At Least One Hypersensitivity TEAE (FMQ Algorithmic)	Neg	0	0	0	0	0	0	1 (4.0)	1 (3.1)
	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	2 (6.1)	2 (4.5)
Patients with At Least One TEAE in Anaphylactic Reaction FMQ (Narrow)	Neg	0	0	0	0	0	0	0	0
	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	1 (3.0)	1 (2.3)
Patients with At Least One TEAE in AKI FMQ (Narrow)	Neg	0	0	0	0	0	0	0	0
	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	0	0
Patients with At Least One TEAE in AKI FMQ (Broad)	Neg	3 (7.1)	1 (2.6)	1 (2.7)	2 (2.6)	0	0	1 (4.0)	1 (3.1)
	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	1 (3.0)	1 (2.3)
Patients with At Least One TEAE, Serious TEAE, Drug-related TEAE, Fatal TEAE, and/or TEAE Leading to Treatment Discontinuation in Hepatic Injury and Hepatic Failure FMQ (Narrow)	Neg	1 (2.4)	2 (5.1)	4 (10.8)	6 (7.9)	1 (7.1)	0	1 (4.0)	1 (3.1)
	TU	2 (13.3)	1 (12.5)	0	1 (5.9)	1 (11.1)	0	0	0
	TE	0	1 (3.1)	1 (3.0)	2 (3.1)	0	0	2 (6.1)	2 (4.5)
Patients with At Least One Injection Site Reaction (ISR)	Neg	0	6 (15.4)	2 (5.4)	8 (10.5)	0	0	2 (8.0)	2 (6.3)
	TU	2 (13.3)	1 (12.5)	2 (22.2)	3 (17.6)	2 (22.2)	0	1 (12.5)	1 (9.1)
	TE	0	6 (18.8)	2 (6.1)	8 (12.3)	0	4 (36.4)	8 (24.2)	12 (27.3)
Patients with At Least One Flu-like Reaction (FLR 1), Adverse Events with PTs Including Influenza like illness, Pyrexia, Feeling hot, Body temperature increased, Chills, Myalgia, or Arthralgia, Starting on the Day of Injection or Next Day.	Neg	0	0	0	0	0	0	0	0
	TU	0	1 (12.5)	1 (11.1)	2 (11.8)	0	0	2 (25.0)	2 (18.2)
	TE	0	0	0	0	0	1 (9.1)	5 (15.2)	6 (13.6)
	Neg	0	0	0	0	0	0	0	0

	ADA Category	Pool 1 Study CS3 + Study CS8				Pool 4 Study CS3 + Study CS7 + Study CS13			
			Olezarsen				Olezarsen		
	Neg TU TE	Placebo (N = 42) (N = 15) (N = 5) n (%)	50 mg (N = 39) (N = 8) (N = 32) n (%)	80 mg (N = 37) (N = 9) (N = 33) n (%)	Total Olezarsen (N = 76) (N = 17) (N = 65) n (%)	Placebo (N = 14) (N = 9) (N = 0) n (%)	50 mg/ 80 mg (N = 7) (N = 3) (N = 11) n (%)	80 mg (N = 25) (N = 8) (N = 33) n (%)	Total Olezarsen (N = 32) (N = 11) (N = 44) n (%)
Patients with At Least One Flu-like Reaction (FLR 2), Adverse Events with PTs Including Either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, Plus At Least Two of the Following Symptoms with PTs: Chills, Myalgia, or Arthralgia, Starting on Day of Injection or the Next Day.	TU	0	0	0	0	0	0	0	0
	TE	0	0	0	0	0	0	0	0
Patients with At Least One Adjudicated Treatment-emergent Pancreatitis Event	Neg	3 (7.1)	1 (2.6)	0	1 (1.3)	3 (21.4)	1 (14.3)	0	1 (3.1)
	TU	4 (26.7)	0	0	0	4 (44.4)	0	1 (12.5)	1 (9.1)
	TE	0	0	1 (3.0)	1 (1.5)	0	0	2 (6.1)	2 (4.5)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8)
Pool 4: All FCS population studies (CS3 + CS13 + CS7)
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: Analysis based on data collected while study drug is administered until the day of the patient's last contact date within the study.
Note: Treatment-Emergent ADA: patients with either treatment-induced ADA or treatment-boosted ADA; 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 IM sample results during the Treatment and Post-Treatment Evaluation Periods are negative and have at least one evaluable IM result collected after the first dose of study drug.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For the summarization of number of patients (n), a patient was counted only once even if > 1 event was reported. A patient was classified according to the worst reported severity if > 1 event was reported.
Abbreviations: ADA = Anti-drug Antibodies; AE = adverse event; AKI = acute kidney injury; CMH = Cochran-Mantel-Haenszel; FCS = familial chylomicronemia syndrome; FLR = flu like reaction; FMQ = FDA MedDRA query; HLT = high level term; IM = immunogenicity; ISR = Injection Site Reactions; Neg = negative ADA; PT = preferred term; TE = treatment-emergent ADA; TEAE = treatment-emergent adverse event; TU = treatment-unaffected AD

2.5.8.8. Safety related to drug-drug interactions and other interactions

2.5.8.8.1. Drug- drug interactions

No clinical drug-drug interaction studies have been conducted with olezarsen.

Considering that olezarsen is not a substrate/inducer/inhibitor for the classic CYP oxidative metabolic pathways or for the major drug transporters and given that the in vitro results did not demonstrate drug-drug interactions on plasma protein binding, olezarsen has a very low potential to have drug-drug interactions with drugs that utilize CYP pathways, transporters, or are highly plasma protein-bound.

2.5.8.8.2. Use in Pregnancy and Lactation

One patient in the olezarsen 80 mg group reported a partner pregnancy in study CS3. No pregnancies were reported in the other treatment groups or in other studies. The male infant was born full-term via elective caesarian delivery with no known birth defects noted at that time. On an unknown date, the Investigator indicated that "the baby is developing normally but a MR scan was performed to control macrocephaly".

A fertility assessment (Seg I) mouse study was completed with olezarsen and showed the absence of any fertility and early embryonic development toxicity. Thus, there is little to no risk for untoward reproductive or developmental effects in woman of child-bearing potential.

2.5.8.8.3. Overdose

As of the cutoff date, no patients treated with olezarsen have experienced an overdose.

2.5.8.8.4. Drug Abuse

There have been no reports of patient abuse or dependence on olezarsen. Olezarsen does not cross the blood-brain barrier and has no known effects on the central nervous system (CNS). Therefore, there is little, if any potential for abuse or dependence.

2.5.8.8.5. Withdrawal and Rebound

Olezarsen has no known effects on the CNS. Withdrawal effects would not be expected because olezarsen does not cross the blood-brain barrier. There is insufficient information to evaluate rebound in the FCS population as nearly all patients rolled into the open-label extension study CS13 and there was a low incidence of permanent study discontinuations. However, based on the long terminal elimination half-life, no rebound effect would be expected.

2.5.8.8.6. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Impairment of mental ability and effects on the ability to drive or operate machinery are not expected as olezarsen does not cross the blood-brain barrier.

2.5.8.9. Discontinuation due to adverse events

Pool 1 (CS3+ CS8)

Table 91: Treatment-Emergent Adverse Events Leading to Permanent Study Drug Discontinuation by System Organ Class and Preferred Term (CS3, CS8, and Pool 1)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Patients with At Least One TEAE Leading to Treatment Discontinuation	0	1 (4.8)	2 (9.1)	3 (7.0)	0	8 (13.8)	3 (5.3)	11 (9.6)	0	9 (11.0)	5 (6.4)	14 (8.8)
General disorders and administration site conditions												
Injection site erythema	0	0	0	0	0	2 (3.4)	0	2 (1.7)	0	2 (2.4)	0	2 (1.2)
Injection site haemorrhage	0	0	0	0	0	2 (3.4)	0	2 (1.7)	0	2 (2.4)	0	2 (1.2)
Chest discomfort	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Chills	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Death	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Fatigue	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Injection site pruritus	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Injection site urticaria	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Sudden death	0	1 (4.8)	0	1 (2.3)	0	0	0	0	0	1 (1.5)	0	1 (0.7)
Gastrointestinal disorders												
Abdominal pain	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Abdominal pain lower	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Diarrhoea	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Dyschezia	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Gastrooesophageal reflux disease	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Vomiting	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)

System Organ Class Preferred Term	Study CS3				Study CS8				Pool 1 Study CS3 + Study CS8			
		Olezarsen				Olezarsen				Olezarsen		
	Placebo (N = 23)	50 mg (N = 21)	80 mg (N = 22)	Total Olezarsen (N = 43)	Placebo (N = 39)	50 mg (N = 58)	80 mg (N = 57)	Total Olezarsen (N = 115)	Placebo (N = 62)	50 mg (N = 79)	80 mg (N = 79)	Total Olezarsen (N = 158)
Investigations												
Liver function test increased	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Urine protein/creatinine ratio abnormal	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Vascular disorders												
Flushing	0	0	1 (4.5)	1 (2.3)	0	0	1 (1.8)	1 (0.9)	0	0	2 (2.6)	2 (1.3)
Cardiac disorders												
Atrial fibrillation	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)
Musculoskeletal and connective tissue disorders												
Myalgia	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Trismus	0	0	1 (4.5)	1 (2.3)	0	0	0	0	0	0	1 (1.4)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Squamous cell carcinoma of head and neck	0	0	0	0	0	0	1 (1.8)	1 (0.9)	0	0	1 (1.2)	1 (0.6)
Nervous system disorders												
Headache	0	0	0	0	0	1 (1.7)	0	1 (0.9)	0	1 (1.2)	0	1 (0.6)

Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled studies (CS3 + CS8).
Note: N = number of safety patients in treatment group; n = number of patients in the specified category; % = n/N × 100.
Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if > 1 event was reported.
Note: Pooled proportions are adjusted by study using the CMH method. The weights used in the adjustment are 0.307 and 0.693 for CS3 and CS8, respectively.

Abbreviations: AE = adverse event; CMH = Cochran-Mantel-Haenszel; TEAE = treatment-emergent adverse event

Pool 4 (CS3 + CS13 + CS7)

Across all FCS population studies, 7 (10.6%) patients in the olezarsen 80 mg group and 1 (4.8%) patient in the olezarsen 50 mg/80 mg group experienced a TEAE that led to permanent study drug discontinuation; no patient in the placebo group discontinued from the study due to a TEAE.

Table 92: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term Safety Set – Pool 4 (CS3, CS7, and CS13)

System Organ Class/Preferred Term	**Placebo (N=23) n (%) Events**	**Olezarsen 50mg/80mg (N=21) n (%) Events**	**Olezarsen 80mg (N=66) n (%) Events**	**Total Olezarsen (N=87) n (%) Events**
Patients with any TEAEs Leading to Treatment Discontinuation	***0***	***1 (4.8) 1***	***7 (10.6) 12***	***8 (9.2) 13***
General disorders and administration site conditions	**0**	**1 (4.8) 1**	**2 (3.0) 2**	**3 (3.4) 3**
Chest discomfort	0	0	1 (1.5) 1	1 (1.1) 1
Chills	0	0	1 (1.5) 1	1 (1.1) 1
Sudden death	0	1 (4.8) 1	0	1 (1.1) 1
Immune system disorders	**0**	**0**	**3 (4.5) 3**	**3 (3.4) 3**
Hypersensitivity	0	0	2 (3.0) 2	2 (2.3) 2
Anaphylactic reaction	0	0	1 (1.5) 1	1 (1.1) 1
Gastrointestinal disorders	**0**	**0**	**2 (3.0) 3**	**2 (2.3) 3**
Diarrhoea	0	0	1 (1.5) 1	1 (1.1) 1
Pancreatitis	0	0	1 (1.5) 1	1 (1.1) 1
Vomiting	0	0	1 (1.5) 1	1 (1.1) 1
Investigations	**0**	**0**	**1 (1.5) 1**	**1 (1.1) 1**
Hepatic enzyme increased	0	0	1 (1.5) 1	1 (1.1) 1
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (1.5) 2**	**1 (1.1) 2**
Myalgia	0	0	1 (1.5) 1	1 (1.1) 1
Trismus	0	0	1 (1.5) 1	1 (1.1) 1
Vascular disorders	**0**	**0**	**1 (1.5) 1**	**1 (1.1) 1**
Flushing	0	0	1 (1.5) 1	1 (1.1) 1

N = number of safety patients in treatment group; n = number of patients in the specified category; %=n/N*100.

Pool 5 (CS3 + CS13 + CS7 + CS2 + CS8)

Overall, 10 (8.1%) patients in the olezarsen 80 mg group, 9 (8.9%) patients in the olezarsen 50 mg/80 mg group, 2 (2.9%) patients in the olezarsen 10-40 mg group, and 1 (1.2%) patient in the placebo group experienced a TEAE that led to permanent study drug discontinuation.

2.5.8.10. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

Olezarsen is a 2'-O-methoxyethyl (MOE) chimeric antisense oligonucleotide (ASO) covalently bound to GalNAc3, a high affinity ligand for the hepatocyte-specific asialoglycoprotein receptor. The ASO portion of olezarsen is the parent drug, volanesorsen, and is designed to bind to the human apolipoprotein C-III (apoC-III) mRNA. The GalNAc3 conjugate should increase the uptake of the ASO to hepatocytes, thereby decreasing the dose of olezarsen needed to reduce apoC-III over its non-conjugated parent, volanesorsen. Therefore, Tryngolza contains the same active molecule as Waylivra (volanesorsen), already approved in EU for the same indication, but it is expected to be delivered mainly to the liver. This should determine a lower systemic exposure to the active molecule volanesorsen and thus lower incidence of off-target AEs.

The safety dataset is mainly based upon phase 2 and 3 studies: in particular three phase 3 studies in patients with FCS: 1) a double-blind, placebo-controlled study (ISIS 678354-CS3, hereafter referred to as CS3); 2) an open-label extension of this study (ISIS 678354-CS13, hereafter referred to as CS13); and 3) an open-label safety study in patients previously treated with volanesorsen, switched to olezarsen (ISIS 678354-CS7, hereafter referred to as CS7). Additional safety data are included from trials in patients with hypertriglyceridemia: in particular, study CS8 was a trial in patients with hyperglyceridaemia, that enrolled a total of 154 patients randomly assigned to treatment, of these, 130 patients completed study drug (50 in the olezarsen 80 mg group, 44 in the olezarsen 50 mg group, and 36 in the placebo group). Moreover, given the limited number of patients enrolled (due to the rarity of the condition), the applicant analysed safety data using several pooling datasets of the single studies (in some pooling datasets, patients with hyperglyceridaemia were included). The main pooling datasets were: Pool 1 (Pivotal FSC study and hyperglyceridaemia study: randomized, double-blind, placebo controlled studies, CS3 + CS8); Pool 2 (Randomized, double-blind, placebo-controlled study in FCS + hypertriglyceridemia and atherosclerotic cardiovascular disease, or severe hypertriglyceridemia population, CS3 + CS8 + CS2). Pool 3 (Long-term open-label studies in FCS population, CS7 + CS13). Pool 4 (All FCS population studies, CS3 + CS13 + CS7). Pool 5 (All patient population studies, CS3 + CS13 + CS7 + CS2 + CS8)

In this discussion, main focus is on data from CS3 and Pool 4, i.e., FCS patients, and also, from Pool 1. To be noted, that in the following sections, AE means TEAE. Since the intended dose is 80 mg, where no mention is made, data are referred to this dose.

The population enrolled in the pivotal trial CS3 consisted of patients with 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, GPIHBP1, APOA5, APOC2, GPD1, or LMF1). Baseline characteristics were balanced in CS3/Pool 4; the only important issue is the presence of very few subjects > 65 years in Pool 4 (n=6, 1, 3, in 80 mg, 50 mg, placebo, respectively). There were some inevitable unbalances (since the small numbers) in the use of a few concomitant medicines. Probably, the most important of these drugs is acetylsalicylic acid (due to its impact on platelet function) which showed a marked unbalance in that it was used more often in placebo arm of the pivotal CS3 study (9.1% in 80 mg, 4.8% in 50 mg, 26.1% in placebo).

Exposure

In total, 378 patients participated in clinical development programme of olezarsen. Of them, 292 patients received at least 1 dose of olezarsen, and 123 of them received recommended 80 mg dose. In all 5 studies, 245 patients were exposed to study treatment for 12 months or more (up to 36 months).

Since the rarity of the disorder, patients in CS3 were very few: n=22, 21, 23 in 80 mg, 50 mg and placebo respectively. In Pool 4, the 80 mg group had 66 patients. In the pivotal study CS3, the mean durations of treatment were almost similar across arms, but a slight longer exposure to placebo can be seen, confirming the slightly higher discontinuation rate in the active treatment arms (323.4 days in the olezarsen 80 mg, 339.3 days in the olezarsen 50 mg, and 353.1 days in the placebo).

Adverse events, serious adverse events and deaths

Across all studies and pools, the proportion of patients with AEs was similar (or greater) in the placebo group compared with the olezarsen arms (in the pivotal study CS3, the proportion of patients with AEs was: 86.4% in olezarsen 80 mg; 85.7% in olezarsen 50 mg; and 95.7% in placebo). However, the proportion of patients who experienced AEs related to study drug was greater in the olezarsen treatment groups compared with the placebo. The majority of AEs experienced by patients in all treatment groups were mild or moderate in severity, and the proportion of patients who experienced serious AEs was similar or greater in the placebo group compared with the olezarsen treatment groups.

In the pivotal study CS3, in olezarsen 80 mg (the intended use dose) vs placebo, the most frequent AEs were abdominal pain (18.2% vs 34.8%), COVID 19 (13.6% vs 34.8%), platelet count decreased (13.6% vs 4.3%), pain in extremity (13.6% vs 4.3%), anaemia (n=2, 9.1%, vs n=1, 4.3%), abdominal distention (9.1% vs 0%), abdominal pain upper (9.1% vs 4.3%), diarrhoea (9.1% vs 26.1%), vomiting (9.1% vs 0%), injection site erythema (9.1% vs 4.3%), and cough (9.1% vs 8.7%). Absolute numbers are very small; for instance, 1 patient was equivalent to 4.3% of the arm and 2 patients were 9.1%, thus the smallest possible fluctuation, corresponding to 1 patient, was able to double the prevalence of a given AE, making the interpretation of the differences between arms very difficult.

In Pool 1, in the olezarsen 80 mg group, the most frequently experienced AEs were COVID-19 (9.0%); abdominal pain (8.0%); pain in extremity (6.6%); cough (6.4%); platelet count decreased (5.4%); anaemia and injection site erythema (5.2% each); and alanine aminotransferase increased, urinary tract infection, and nasopharyngitis (5.0% each). Again, the sample size was small.

In Pool 1: Injection site erythema was more frequent in olezarsen arms than placebo: 5.2% in 80 mg, 11.0% in 50 mg, 1.3% in placebo; this AE has been reflected in SmPC.

In pool 4, olezarsen 80 mg group, 87.9% experienced at least one AE, comparing with 95.7% in placebo group. The most common AEs in olezarsen 80 mg group were COVID-19 (19.7%), Injection site erythema (16.7%), Oropharyngeal pain (12.1%), Injection site discolouration, Nausea and Vomiting (10.6% each), and Influenza (9.1%). The most common ADRs in olezarsen 80 mg group were Injection site erythema (15.2% vs 4.3% in placebo group), Injection site discolouration (10.6% vs 4.3% in placebo group), Myalgia (7.6% vs 0 in placebo group), Chills and Injection site swelling (6.1% each vs 0 in placebo group), Vomiting and headache (4.5% each vs 0 in placebo group), Injection site pain and Hypersensitivity (3% each vs 0 in placebo group).

In the SmPC section 4.8 Applicant stated: *In a combined analysis from three clinical trials including Balance and 2 open-label studies (CS7 and CS13) in patients with FCS (N = 89), the following adverse*

reactions were reported in patients treated with olezarsen: injection site erythema (17%), chills (7%), myalgia (7%), injection site pain (6%), and hypersensitivity (2%).

Severity: in Pool 1 (CS3 + CS8) the majority of patients experienced AEs that were mild or moderate in severity. The proportion of patients who experienced mild AEs was similar across treatment groups (38.3%, 34.7%, and 34.2% in the olezarsen 80 mg, 50 mg, and the placebo group, respectively). AEs classified as severe were similar in numbers across the arms (5% in 80 mg, 8% in 50 mg, 13.8% in placebo).

The severe events in olezarsen 80 mg group (n=4, 5.0%) were drug withdrawal syndrome, cellulitis, sepsis, tibia fracture, encephalopathy, non-Hodgkin's lymphoma, lacunar infarction and pancreatitis. These severe AEs were assessed as serious and not related (or unlikely related) to the study drug. In olezarsen 50 mg, (n=6, 8.0%), atrial fibrillation, death, sepsis, urinary tract infection, sudden death, gastroenteritis bacterial, and intentional overdose. These severe AEs were mostly assessed as serious and not related (or unlikely related) to study drug.

Anaphylactic reaction was described in 1 subject (1.3%) in Pool 3 (long-term) with olezarsen 80 mg, while hypersensitivity in the same Pool was seen in 2 (3.8%) subjects in the same arm.

AEs related to study drug. In Pool 1, more patients experienced at least one related TEAE with olezarsen compared to placebo, but with no clear dose-dependency (19.5% in 80 mg, 27.9% in 50 mg and 12.0% in placebo). The most common SOC was General disorders and administration site conditions. Platelet count decreased was more frequent in 80 mg (n=4/79, 5.4%) than 50 mg (n=1/79, 1.5%) or placebo (n=1/62, 1.3%).

Serious Adverse Events (SAEs). SAEs were similar with olezarsen than placebo (in Pool 1: 13.9% in 80 mg, 13.0% in 50 mg, 15.6% in placebo). SAEs of Cardiac disorders were more frequent in olezarsen (no events occurred in placebo and a few of events occurred in olezarsen). SAEs of Gastrointestinal disorders occurred more frequently with placebo, in particular for pancreatitis.

In Pool 4, a lower proportion of patients in the olezarsen 80 mg group (16.7%) experienced serious TEAEs compared with the placebo group (39.1%). Different types of pancreatitis contributing significantly to the larger number of SAEs in the placebo group.

Deaths. In the pivotal study CS3, one subject died in the 50 mg arm for sudden death (unknown origin): a 74-year-old female who had received 2 doses of olezarsen 50 mg and died suddenly on Study Day 42 with no preceding symptoms. The sudden death was considered unlikely related to study drug by the Investigator and Sponsor, and the MACE adjudication committee determined that this event was a MACE.

In the study CS8, one subject died in the 50 mg arm for sudden death (unknown origin): 76-year-old male, experienced a severe serious TEAE leading to death on Study Day 206, 5 weeks after the last dose of olezarsen. The patient had ongoing coronary artery disease, cardiac pacemaker, hypertension, hyperlipidemia under statin treatment, Type 2 diabetes, former smoker. The MACE adjudication committee were unable to determine if the event was a myocardial infarction or heart failure. The event was only adjudicated as death and was assessed as not related to study drug.

In study CS2, one patient in the olezarsen 15 mg every 2 weeks group died due to a serious TEAE of cardiac arrest, which was assessed as unlikely related to study drug by the Investigator and Sponsor (Patient 0109-002). A 63-year-old male died on Study Day 90, 5 days after the last dose of olezarsen. The cause of death was reported as "heart-related". Relevant cardiovascular history included type 2 diabetes, dyslipidemia, family history of CAD, hypercholesterolemia, hypertriglyceridemia, carotid artery disease, acute MI, coronary artery bypass graft, coronary revascularization, documented CAD, ST-segment elevation MI, unstable angina, heart failure, hypertension, aortic stenosis, and valvular heart disease. The event was assessed as unlikely related to study drug.

Thus, in the 3 patients died, based on the narratives provided, the most likely mechanism of death was cardiac in nature; two patients also had a clear history of CV disorders, making this diagnosis even more plausible. In principle it could be accepted that a relationship to olezarsen appears not likely; however, all the three deaths occurred in patient treated with olezarsen and no deaths occurred in placebo. The small numbers and the confounding factors (i.e. previous CV risk factors) make any final conclusions difficult to be drawn, but the applicant should implement routine pharmacovigilance measures for CV events in patients treated with olezarsen.

In the light of the SAEs of CV events and of the observed sudden deaths (all of these events were observed in olezarsen arms of Pool 1 and none in placebo) the applicant was requested to discuss in more details the possible relationship of CV events and sudden deaths with olezarsen, also taking account baseline characteristics and pre-existing CV risk factors**.** In its response, the applicant did not consider that the frequency of CV events warranted the adding of "CV events", or similar terms, to the 4.8 section of SmPC. However, as it can be seen in the table below, when pooling more patients from several studies, it seems that CV events were more frequent with olezarsen compared to placebo. The difference is small, the populations are not completely overlapping for baseline characteristics and diagnosis, in some subgroups (e.g. olezarsen 80 mg) the frequency was similar, and in some cases possible confounding factors cannot be ruled out; therefore, firm conclusions are difficult to be drawn. Thus, the applicant should monitor carefully this kind of events with pharmacovigilance activities.

Table 93: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Set – Pool 5

System Organ Class/ Preferred Term	Placebo (N=86) n (%)		Olezarsen 10-40 mg (N= 69) n (%)		Olezarsen 50 mg/80 mg (N=101) n (%)		Olezarsen 80 mg (N=123) n (%)		Total Olezarsen (N=292) n (%)	
Patients with any TEAEs	72 (83.7)	369	63 (92.6)	435	84 (83.2)	544	96 (78.0)	654	243 (83.2)	1633
Blood and lymphatic system disorders	7 (8.1)	9	5 (7.4)	5	5 (5.0)	6	6 (4.9)	8	16 (5.5)	19
Anaemia	1 (1.2)	1	4 (5.9)	4	2 (2.0)	2	4 (3.3)	5	10 (3.4)	11
Iron deficiency anaemia	1 (1.2)	1	0		2 (2.0)	2	1 (0.8)	1	3 (1.0)	3
Thrombocytopenia	0		1 (1.5)	1	1 (1.0)	1	1 (0.8)	1	3 (1.0)	3
Hypochromic anaemia	0		0		0		1 (0.8)	1	1 (0.3)	1
Leukocytosis	1 (1.2)	2	0		1 (1.0)	1	0		1 (0.3)	1
Anaemia vitamin B12 deficiency	1 (1.2)	1	0		0		0		0	
Eosinophilia	1 (1.2)	1	0		0		0		0	
Increased tendency to bruise	1 (1.2)	1	0		0		0		0	
Lymphopenia	1 (1.2)	1	0		0		0		0	
Microcytic anaemia	1 (1.2)	1	0		0		0		0	
Cardiac disorders	4 (4.7)	4	7 (10.3)	8	10 (9.9)	17	5 (4.1)	5	22 (7.5)	30
Acute myocardial infarction	0		0		2 (2.0)	2	0		2 (0.7)	2
Angina pectoris	1 (1.2)	1	0		1 (1.0)	1	1 (0.8)	1	2 (0.7)	2
Atrial fibrillation	1 (1.2)	1	0		1 (1.0)	2	0		1 (0.3)	2
Bradycardia	0		0		2 (2.0)	2	0		2 (0.7)	2
Bundle branch block right	1 (1.2)	1	2 (2.9)	2	0		0		2 (0.7)	2
Tachycardia	0		0		1 (1.0)	1	1 (0.8)	1	2 (0.7)	2
Acute coronary syndrome	0		1 (1.5)	1	0		0		1 (0.3)	1
Angina unstable	0		1 (1.5)	1	0		0		1 (0.3)	1
Arrhythmia	0		0		1 (1.0)	1	0		1 (0.3)	1

Input data set: ADAE
Program name: t_tese_socpt_p3.sas Run date: 16FEB2024 11:59 Database last modified: 21OCT2023

<u>*AEs of special interest*</u>

AEs of special interest as well as other AEs of interest were identified based on known safety concerns of ASO class.

AESI 1: severe reductions in platelet count (< 50,000/mm3) accompanied by a major bleeding event or clinically relevant non-major bleeding event, or platelet count of < 25,000/mm3 independent of a major bleeding or clinically relevant non-major bleeding event. No patients experienced this AESI across all 5 clinical trials.

AESI 2: requirement of any use of medications (prophylactic treatment, such as antihistamines, acetaminophen, non-steroidal anti-inflammatory drugs, corticosteroids, etc.) as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction. One patient in study CS13 using olezarsen 80 mg experienced anaphylactic reaction which was assessed as serious ADR. The medications the patient received as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction included paracetamol, prednisone, and famotidine. According to the applicant, symptoms reported by the investigator do not exactly match the definition of anaphylactic reaction described in World Allergy Organization Anaphylaxis Guidance 2020, therefore there is no need to add anaphylactic reaction to section 4.8 of SmPC (of note, hypersensitivity is already added there). It may be considered acceptable.

<u>*Other Adverse Events of Interest (OAEI)*</u>

The OAEIs include:

Injection site reactions (ISR). Injection site reactions were more frequent with olezarsen than placebo, but with no clear dose-dependency (in Pool 1: 7.8% in 80 mg, 16.3% in 50 mg, 2.7% in placebo). In the LoQ, the applicant was requested to discuss (and in case implement) whether instructions about how to reduce the incidence or manage the Injection site reactions should be added to the SmPC (e.g. Waylivra has instructions about rotating the injection site)**.**

In Pool 4, any ISR occurred in 11 (16.7%) patients in olezarsen 80 mg group, comparing with 2 (8.7%) in the placebo group. Of most frequent ISRs in olezarsen 80 mg group were Injection site erythema, Injection site discolouration, Injection site swelling and Injection site pain.
All reactions were mild or moderate in severity and none resulted in permanent discontinuation or dose reduction of olezarsen in patients with FCS.

Local cutaneous reactions at the injection site. In the study CS8, four patients (6.9%) in the olezarsen 50 mg group experienced at least 1 injection site reaction; all 4 patients discontinued the study drug as a result of these events. There were no serious or severe reactions. No patient in the olezarsen 80 mg or placebo groups experienced this AE during the study. The mean (SD) time to onset of the first injection site reaction in the olezarsen 50 mg group was 62.5 (55.25) days. The mean (SD) duration of the event was 143.6 (143.54) days. The mean (SD) number of injections received before the first LCRIS was 3.0 (2.16).
In Pool 4, 1 (1.5%) patient in the olezarsen 80 mg group experienced OAEI of LCRIS per definition A. No patients experienced LCRIS in placebo group. There were no LCRIS per definition B.
Therefore, injections site reactions were observed with olezarsen: In the LoQ, the applicant was requested to propose a text, in both SmPC and PL, for managing ISRs after their onset.

With their response, the applicant has added a subsection "Description of selected adverse reactions" with the instruction on how to manage the ISRs after their onset in section 4.8 of the SmPC and corresponding section of PL. The wording is acceptable.

Flu-like reactions. In Pool 4, 7 (10.6%) patients in the olezarsen 80 mg group experienced FLR 1 compared with 0 patient in the placebo group. No patients in any treatment group experienced FLR 2. The most frequesnt FLRs in olezarsen 80 mg group were arthralgia, chills, and myalgia.

Bleeding events. in Pool 1, the incidence of patients with at least one bleeding was similar across the arms (9.2% in 80 mg, 8.0% in 50 mg, 8.9% in placebo).
In Pool 4, 8 (12.1%) patients in the olezarsen 80 mg group experienced any bleeding AE compared with 4 (17.4%) patients in the placebo group. Overall, most of the bleeding AEs were non-serious, mild or moderate in severity. This data was confirmed also by other pools, suggesting that bleeding risk with olezarsen is low and comparable with placebo.

Thrombocytopenia events (including platelet count decreases). In study CS3, a greater proportion of patients in the olezarsen 80 mg (59.1%) and olezarsen 50 mg (52.4%) experienced 2 occurrences of platelet counts below the lower limit of normal (140,000/mm3) and/or a single occurrence of platelet count below 100,000/mm3, compared with placebo (30.4%). Additionally, a greater proportion of patients in the olezarsen 80 mg group (50%) and olezarsen 50 mg (42.9%) experienced a platelet count reduction of at least 30% from Baseline compared with the placebo (30.4%). However, a comparable proportion of placebo patients (13%) experienced a platelet count reduction of at least 50% compared with the olezarsen 80 mg group (9.1%) and the olezarsen 50 mg group (9.5%). From the graphs plotting the mean percentage change of platelet count from baseline (in study CS3) it emerges that placebo is associated with an increase in platelet count (about 20%), whereas in both olezarsen arms there is a decrease of about 14%.

In Pool 4, percentage of patients with any Thrombocytopenia TEAEs was similar between olezarsen 80 mg and placebo groups (3 (4.5%) vs 1 (4.3%), respectively.
To summarise: no AESIs of severe platelet count reductions were reported in any individual clinical studies. No patients met the predefined stopping rule regarding platelet counts or discontinued treatment due to thrombocytopenia AEs. A greater proportion of patients in olezarsen experienced platelet reductions of ≥30% from Baseline or to counts in the range of >75,000 to <140,000/mm3 compared with the placebo; however, the proportion of patients who experienced platelet reductions of >50% or counts <75,000/mm3 was similar between both olezarsen groups and the placebo, and no patient in olezarsen arms experienced a platelet count of <50,000/mm3. It has been observed a greater decrease in platelet count in the CS8 study when exposure-response relation is analysed.
In Pool 1 and study CS3, more patients with at least 1 Thrombocytopenia AE were detected in olezarsen 80 mg group, compared with placebo. Taken together, the TEAE and laboratory data for Pool 5 do not suggest that olezarsen has a clinically meaningful effect on platelet count. Olezarsen seems to be associated with a mild reduction of platelet count, apparently dose-related; the level of platelet count remained within safety margins in the clinical trials. However, since the treatment is intended for chronic administration, and since a very small number of patients have been exposed in the intended indication, it is not clear if a more severe platelet reduction could occur with long-term use. Therefore, the applicant was requested to discuss the opportunity to implement a monitoring plan in the SmPC for this AE. Although keeping in mind that laboratory tests were consistent across different pools and showed more frequent mild to moderate platelet count decrease from baseline in olezarsen 80 mg group vs placebo group as well as the fact that thrombocytopenia is known class effect, the applicant was requested to consider adding platelet count decrease to SmPC section 4.8.

In their response, with regards to platelet monitoring, after review of the platelet data in the Pool 4 FCS trials, the applicant concluded that the platelet count decreases in olezarsen-treated patients were not clinically meaningful and did not warrant a warning on platelet monitoring. The rationale is based on the following:

- No worsening in severity of platelet count reductions over time. Subjects mostly experienced fluctuations with excursions below the lower limit of normal, with no sustained progression of the decrease in platelet counts.
- No observations of severe platelet count reduction (< 50,000 mm^3) in subjects in the olezarsen 80 mg group.
- Return of platelets to within normal range, baseline values, or > 100,000 mm^3 over time while in the on-treatment period without permanent study drug discontinuations.
- Percentage of subjects with > 50% platelet count reduction from baseline as comparable between placebo (3 [13.0%]) and olezarsen 80 mg (n=9 [13.2%]) groups.
- Among subjects with platelet count reductions of ≥ 30% from baseline:
  - Majority had platelet counts within normal range or had nadir platelet count reduction of mild/Grade-1 in severity.
  - 5 subjects (7%) in olezarsen 80 mg and 2 subjects (9%) in the placebo groups had moderate/Grade-2 or worse platelet count reductions (< 75,000 mm^3).

- No severe/Grade-3 (< 50,000 mm^3) platelet count reduction was observed in any subject in the total olezarsen 80 mg group.

- No subject with platelet count < LLN experienced a concurrent serious or severe clinical bleeding event at any time during the study.

- All TEAE of thrombocytopenia reported in the olezarsen treatment groups were mild (n=5) or moderate (n=1) in severity, with transient platelet reductions; no patient met any pre-defined stopping rule regarding platelet counts, and no patient experienced a concurrent serious or severe bleeding event due to the events.

As the applicant does not consider platelet count decreased to be an ADR a warning and precaution on platelet monitoring is not warranted.

The applicant's reasoning to not include platelet count decrease as ADR in SmPC section 4.8 is considered acceptable by the CHMP. From the data provided, olezarsen seems to be associated with a mild reduction of platelet count, apparently dose-related; the level of platelet count remained within safety margins in the clinical trials. On the other side, it must be kept in mind that the treatment is intended for chronic administration, and that a very small number of patients have been exposed during the clinical trials for the intended indication; thus, it is not completely certain that a more severe platelet reduction cannot occur with long-term use. The applicant should continue monitoring this important AE with PV activities.A warning regarding the lack of experience in FCS patients with platelet count <100,000/mm3 is added to the SmPC section 4.4 as safety in regard to platelet count in mentioned patients group is very limited.

Hypersensitivity events. Across the olezarsen clinical trials, the number of patients who experienced hypersensitivity AEs was higher in olezarsen groups. In Pool 4, AEs by Hypersensitivity FMQ (Narrow) occurred in 3 (4.5%) patients in olezarsen 80 mg group, comparing with none in the placebo group. AEs by Hypersensitivity FMQ (Broad) occurred in 9 (13.6%) patients in olezarsen 80 mg group, comparing with 1 (4.3%) in the placebo group. Overall, the incidence of serious hypersensitivity AEs was low and occurred in 3 (2.4%) in FCS patients in the 80 mg group compared with 1 (1.2%) patient in the placebo group and resulted in permanent discontinuation from the study. It was similar to overall olezarsen exposure (3 patients, 1.0%). Of serious events, 2 were severe and 1 was moderate in severity. All serious events were fully reversible with steroids and antihistamines, severe hypotension was not reported for any patients,no epinephrine was used. All serious hypersensitivity AEs occurred in patients with FCS and who were previously treated with volanesorsen. Due to the temporal relationship of the hypersensitivity events with olezarsen administration, and the biological plausibility, hypersensitivity reactions are considered an important risk, and are listed at the SmPC 4.8 section (this is supported).

Renal impairment events (including eGFR decreases and creatinine, UACR, and UPCR increases). Across all 5 studies, the number of patients who experienced any Renal Impairment AEs was lower in olezarsen groups comparing to placebo group. Overall, the patients reaching threshold values for laboratory renal parameters in the olezarsen groups were generally similar or lower comparing with placebo group. In pool 4, any Renal Impairment AEs occurred in 3 (4.5%) patients in olezarsen 80 mg group, compared with 2 (8.7%) in the placebo group. Regarding any AEs by Acute Kidney Injury FMQ (Broad), they occured in 2 (3.0%) patients in olezarsen 80 mg group, compared with none in the placebo group. Values for laboratory renal parameters in the olezarsen 80 mg group were comparing with placebo group, except for UPCR ≥ 2000 mg/g which occured in 2 (3.0%) patients in the olezarsen80 mg group vs none in placebo group. Overall, data do not suggest renal function related safety concerns.

Abnormal liver function events (including ALT, AST, GGT, bilirubin, and ALP increases). No patient experienced Hepatic Failure (narrow FMQ) across the olezarsen clinical trials. Number of patients who experienced Hepatic Injury (narrow FMQ) was similar or lower in olezarsen groups (ranged from 1.5 % in 10-40 mg olezarsen group to 4.9% in olezarsen 80 mg group) comparing to 4.7% in placebo group. In Study CS3, the incidence of ALT or AST ≥ ULN was higher in the placebo group than in the olezarsen treatment groups. In Pool 4, the incidence of ALT or AST elevations in the olezarsen treatment groups was similar or lower comparing with the placebo group. Overall, mean hepatic transaminase levels remained within the reference range across all treatment groups throughout the study. There were no cases of Hy's law identified in any treatment group. Proportions of patients experiencing ALT and AST ≥ 3 × ULN were similar between olezarsen and placebo groups.

CV events. When pooling more patients from several studies, it seems that CV events were more frequent with olezarsen compared to placebo. The difference is small, the populations are not completely overlapping for baseline characteristics and diagnosis, in some subgroups (e.g. olezarsen 80 mg) the frequency was similar, and in some cases possible confounding factors cannot be ruled out: firm conclusions are, thus, difficult to be drawn. Therefore, the applicant did not consider that the frequency of CV events warrants the adding of "CV events" to the 4.8 section of SmPC. The applicant should monitor carefully this kind of events with pharmacovigilance activities.

The applicant claims that the increase in HDL-C of 45% in CS3 and 48% in CS8 on olezarsen 80 mg (not adjusted for placebo) is not considered worrisome in terms of atherogenic risk. However, the HDL-C range observed in these studies at baseline and following treatment was not specified, thus preventing any clinical interpretation of the possible shifting of HDL-C from one risk category to another (i.e. HDL-C <40 mg/dl; between 40-80 mg/dl;>80 mg/dl that were the values for which a U-shaped curve for CV events was reported). In any case, considering the mode of action of the drug and the assumed antiatherogenic effect deriving from apoC-III suppression, it can be agreed that the overall action of olezarsen on atherogenic disease progression would be expected to be protective also considering the lack of an obvious biological plausibility for detrimental effects, based on current knowledge. Nevertheless, the long-term cardiovascular safety of treatment needs to be monitored through pharmacovigilance activity in order to intercept any potential signal arising from the clinical use of the drug in the target population.

Dysglycaemia events which included hypoglycemia, hyperglycaemia, and haemoglobin A1c increases. In Pool 4, lower proportion of patients experienced dysglycaemia-related events (by dysglycaemia FMQ narrow and broad) in the olezarsen 80 mg group (7.6% each) compared with the placebo group (17.4% each). Laboratory data do not suggest that olezarsen has a clinically meaningful effect on glycemic control.

OAEIs of Injection site erythema and Injection site pain, flu-like reactions chills and myalgia were recognised as ADRs and added to SmPC section 4.8.

Discontinuation due to adverse events

Across olezarsen clinical trials, 8.1% patients in 80 mg group and 21 (7.2%) patients treated with any olezarsen dose experienced any AE leading to treatment discontinuation, compared to 1.2% in placebo group: this is a substantial difference. Two discontinuations in the olezarsen 50 mg group were caused by the SAEs leading to death that were considered unlikely or not related to study drug. Two (2.0%) patients in olezarsen 50 mg/80 mg group and 1 (1.5%) patient in the olezarsen 10-40 mg group

experienced a serious AE leading to death. The only other reported AEs leading to discontinuation in patients treated with olezarsen in > 1 patient were injection site erythema and injection site haemorrhage, each experienced by 2 patients in the olezarsen 50 mg group, and flushing, experienced by 2 patients in the olezarsen 80 mg group.

In CS3, 3 patients treated with olezarsen experienced AEs that led to permanent study drug discontinuation, versus no patient in the placebo group. A similar picture was observed in CS8 (3 vs 0). Therefore, in Pool 1, treatment discontinuation due to AEs occurred only in olezarsen arms (6.4% in 80 mg, 11.0% in 50 mg) and no discontinuations occurred in placebo. This is also confirmed by the slightly shorter exposure observed in the active treatment arms (see Exposure section above). The SOCs interested in the discontinuations were General disorders (in particular: administration site AEs) and Gastrointestinal disorders.

In Pool 4, 7 (10.6%) patients in the olezarsen 80 mg group experienced a TEAE that led to permanent study drug discontinuation, compared to 0 patients in the placebo group. The most frequent SOC leading to discontinuation in the olezarsen 80 mg group was Immune system disorders - 3 (4.5%) patients. No alarming pattern is seen in the assessment of the AEs that led to discontinuation of olezarsen.

Safety in special populations

Difference in AEs in regards to extrinsic factors, such as gender, race, ethnicity, age, weight, and baseline diabetic status were assessed in olezarsen clinical trials. In some cases there were AEs that had a higher incidence in one specific group than in the other, such as Gastrointestinal disorders and Abdominal pain in male and female. Abdominal pain was more frequent in female (5(17.9%)) vs male (1 (2.0%)) in olezarsen 80 mg group while in placebo group this AE was slightly less frequent in female group, compared to male ((11.1%) vs 4 (15.4%), respectively). Same pattern was noticed regarding General disorders and administration site conditions, Nervous system disorders. This difference was not seen in the placebo arm. These differences are probably due to the small sample size. The reduced size of the sample is the most plausible explanation.

Across all individual clinical studies, 1 partner pregnancy was reported by a patient in the olezarsen 80 mg group in Study CS3. One patient, a 43-year-old male patient, reported paternal exposure during pregnancy on Study Day 8. The patient’s partner was not taking contraceptive drug. At the time of conception, the patient’s partner was smoking approximately 1 pack of cigarettes per day. The male infant was born full term (via elective caesarian delivery) with no known birth defects noted at that time. On an unknown date, the Investigator indicated that “the baby is developing normally but a MR scan was performed to control macrocephaly”. No further information is available. It is difficult to assess whether there can be any correlations between the paternal exposure to olezarsen and the macrocephaly reported for the infant.

Difference in AEs in regard to extrinsic factors, such as geographic location and previous treatment with volanesorsen were assessed in olezarsen clinical trials. In some cases there were AEs that had a higher incidence in one specific group than in the other, especially in US and nonUS patients in regard to SOC Infections and infestations, or in Europeans and North American patients in regard to Gastrointestinal disorders in Pool 4. Patients that received previous treatment with volanesorsen (mainly in pool 4) showed a slightly higher incidence of AEs compared to never-treated patients,

however, similar as regarding extrinsic factors, it is difficult to draw meaningful conclusions due to small or very different patient numbers in some subgroups.

Safety related to interactions

Olezarsen has a very low potential to have drug-drug interactions as it is not a substrate/inducer/inhibitor for the classic CYP oxidative metabolic pathways or for the major drug transporters. Interaction studies were performed with a different ASO, pelacarsen (with warfarin and clopidogrel), targeting a different molecule; no data has been submitted on these studies but the applicant arguments that these studies provide sufficient reassurance on olesarzen interaction too. This point cannot completely be agreed upon, since the different target, but some PK data provided by the applicant for interaction between olezarsen and platelet aggregation inhibitors, provided at least a partial reassurance.

Little to no risk is expected for untoward reproductive or developmental effects in woman of child-bearing potential, however, there is no experience in treating pregnant or breast-feeding women with olezarsen. There are no patients who experienced overdose identified. Patient abuse or dependence on olezarsen is not expected. There is insufficient information to evaluate withdrawal effects in the FCS population. Rebound effect is not expected based on the pharmacology of the IMP. Impairment of mental ability and effects on the ability to drive or operate machinery are not expected with olezarsen.

Data provided by the applicant on the drug-drug interactions and other interactions above supports the proposed labelling.

Laboratory and other findings

In the study CS8, ALT and AST showed small increases in mean percent change from baseline over time in both olezarsen arms, compared to placebo, through week 17, and remained stable thereafter. Moreover, in some exposure-response studies, there is an increase of transaminases in the highest tertile of exposure. These increases remained within the normal reference range and were not considered clinically meaningful by the applicant. It should be noted that patients with transaminases > 3 x ULN were excluded from the pivotal trial, thus it is not known whether, in patients with more advanced liver disease, transaminases could increase over the ULN.

Across olezarsen clinical trials, no pattern or clinically meaningful trends were identified of olezarsen for hematology or coagulation laboratory parameters.

Overall, there was no clinically meaningful impact of treatment-unaffected or treatment-emergent ADA on the overall TEAE incidence, severity, or seriousness of TEAEs, incidence of AESI, incidence of OAEIs, or in laboratory test results. To be noted however, that small sample sizes limit interpretation of the data.

No formal QTc was conducted. A similar proportion of patients across all treatment groups had a worst post-Baseline QTcF shifts to >480 ms and >500 ms and an increase from Baseline QTcF >60 ms.

The applicant did not foresee any rebound effects after withdrawal, due to the long elimination half-life.

2.5.10. Conclusions on the clinical safety

The safety data on olezarsen for the treatment of FCS are considered reliable, given the design, and presentation of data from the 5 clinical studies. The size of the safety population may be considered as limited, but acceptable considering the rarity of the condition. Subjects >65 years old were very few in the clinical trials and safety information for the elder is missing. Since the mean exposure duration was slightly less than 1 year, long term safety is not well characterized.

The most important safety issues concern the AEs of Hypersensitivity. Overall, the frequency of AEs was similar between olezarsen and placebo; however, platelet count decreased, pain in extremity, some abdominal symptoms and injection site reactions were more frequent with olezarsen than placebo. Treatment discontinuations (due to AEs) were more frequent in the active treatment arm.

Based on clinical trial data, it is not possible to specify what kind of hypersensitivity reactions could be associated with olezarsen treatment: anaphylactic reaction in olezarsen group and imbalance in incidence of rash reactions were reported. Due to the acute nature of hypersensitivity reactions, it is considered that routine pharmacovigilance activities are appropriate for further characterisation of hypersensitivity reactions.

Hepatotoxicity, renal toxicity and thrombocytopenia are considered to be important potential risks.

It is considered that more safety data from a higher number of patients should be obtained in long term use, therefore Long term use is Missing information as well as safety profile in pregnant women.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 94: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity Renal toxicity Thrombocytopenia
Missing information	Use in pregnancy Long term use

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 95: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction targeted follow-up Questionnaire Additional pharmacovigilance activities: • None
Renal Toxicity	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction targeted follow-up Questionnaire Additional pharmacovigilance activities: • None
Thrombocytopenia	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction targeted follow-up Questionnaire Additional pharmacovigilance activities: • None
Use in pregnancy	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Long-term safety	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 19.12.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tryngolza (Olezarsen) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive condition that is present from childhood and is characterized by severe hypertriglyceridemia (HTG), with triglyceride (TG) levels >10 mmol/L (>885 mg/dL). This rare disease has a worldwide estimated prevalence of approximately 1 to 13 per million (up to 3600 patients in the United States) (Khavandi et al. 2018; NORD 2023; Pallazola et al. 2020; Rengarajan et al. 2018; Tripathi et al. 2021; Shamsudeen et al. 2022). Prevalence rates vary depending on geographic region and whether diagnosis was based on genetic testing or clinical criteria alone.

The treatment with Tryngolza (olezarsen) aims to provide an additional treatment option for patients with familial chylomicronemia syndrome.

The rationale for treatment with olezarsen is to reduce plasma TG levels enough to reduce the risk of pancreatitis.

The applicant initially proposed the following indication:

"Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of familial chylomicronemia syndrome (FCS) to reduce triglycerides and the rate of acute pancreatitis events."

The revised proposed indication is: "Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS)".

The recommended dose of olezarsen is 80 mg administered by subcutaneous injection once monthly.

3.1.2. Available therapies and unmet medical need

The effective treatment options for this rare disease –familial chylomicronemia syndrome - are limited. In general, the long-term management of the disease includes following an extremely restrictive low-fat diet and abstinence from alcohol; however, life-long adherence to such a regimen is challenging and is almost never consistently achieved by most patients (Baass et al. 2020). Waylivra (volanesorsen) was approved by the EMA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high-risk for pancreatitis. The safety profile of volanesorsen has been well-defined. However, the risk of thrombocytopenia and bleeding requires regular platelet level monitoring. Renal toxicity has been observed, and injection site reactions have resulted in drug discontinuations. The disease and current management of the disease impact on the quality of life as well as other psychosocial aspects of the patient including food-related anxiety (Davidson et al. 2017). Therefore, FCS is still a disease with a high-unmet medical need for effective treatments with an improved safety profile.

3.1.3. Main clinical studies

Study ISIS 678354-CS3 (Balance study) was a pivotal, randomized, double-blind, placebo-controlled, phase 3 trial administered subcutaneously in patients with Familial Chylomicronemia Syndrome (FCS) to evaluate efficacy and safety of subcutaneously administered olezarsen (AKCEA-APOCIII-LRX). The efficacy evaluation was based on measuring the changes in lipid and apolipoprotein parameters (i.e.,

TG, apoC-III, apoB-48, and non-HDL-C), the incidence rate of acute pancreatitis (adjudicated by a blinded, independent committee according to the Atlanta Classification of acute pancreatitis and as outlined in the Pancreatitis Adjudication Charter), and changes in broader healthcare and patient-reported outcomes.

Safety data are derived from studies ISIS 678354-CS3, ISIS 678354-CS8; ISIS 678354-CS13, ISIS 678354-CS7 and ISIS 678354-CS2. The safety database includes a total of 292 patients.

3.2. Favourable effects

The mean percent change from baseline in fasting triglycerides (mg/dL) at Month 6 was -31.99% LSM (95% CI -49.031, -14.940) in the 80 mg olezarsen group, -10.85% LSM (95% CI -27.797, 6.095) in the 50 mg olezarsen group and 11.52% LSM (95% CI -5.321, 28.356) in the placebo group. The difference in comparison with placebo was -43.50% LSM (95% CI -69.085, -17.921; p=0.0009) in the 80 mg olezarsen group and -22.37% LSM (95% CI -47.200, 2.463; p=0.0775) in the 50 mg olezarsen group.

The majority of subsequent endpoints (secondary efficacy endpoints) in the hierarchical testing sequence had nominally significant results. Reductions in the percent change in fasting apoC-III, apoB-48, non-HDL-C at Month 6 and were consistently seen in both olezarsen groups at Month 12 compared with placebo.

Adjudicated acute pancreatitis event rate from week 1 to week 53 was significantly lower in the olezarsen pooled group compared with placebo. Mean event rate/100 patient year was 4.37 (95% CI 0.942-20.298) in the pooled olezarsen group and 36.31 (95% CI 14.700, 89.685) in the placebo group. The mean rate ratio olezarsen-placebo was 0.12 (95% CII 0.022, 0.656; $_{\text{nominal}}$p=0.0144).

3.3. Uncertainties and limitations about favourable effects

The efficacy and safety of olezarsen 80 mg was demonstrated in adults with genetically confirmed familial chylomicronemia syndrome, who were on the maintenance dose of lipid lowering therapy and had a high risk of pancreatitis development. The primary analysis showed that the estimated fasting TG levels from baseline to Month 6 decreased by 43.5% with olezarsen 80 mg compared to placebo. This was considered statistically significant. No statistically significant decrease in fasting TG level from baseline to Month 6 was observed in patients treated with 50 mg of olezarsen. A minority of treated patients (approximately 14% of patients) reached the pre-defined TG level of < 500 - 880 mg/dL. The rate of adjudicated acute pancreatitis was shown to be lower in the pooled olezarsen groups compared to placebo (4.7% vs 36.31% respectively). It was considered that the demonstrated trend towards a reduction in the incidence of pancreatitis at week 53 provided support to the claim of clinical relevance of the treatment effect.

Based on the results from the Balance study, the decrease in fasting TG levels reduces the rate of acute pancreatitis (AP). High chylomicron levels are known to trigger acute pancreatitis. The risk of acute pancreatitis increases by 3% to 4% with each incremental increase of 100 mg/dL in TG levels (dePretis et al. 2018). Consequently, any decrease in fasting TG level even within a limited timeframe is expected to reduce the risk of pancreatitis in patients with FCS. The mean event rate of acute pancreatitis event in the pooled olezarsen group (80 mg +50 mg) was significantly lower compared with placebo group: 4.37/100 pts year (95% CI 0.942- 20.298) and 36.3/ 100 pts year (95% CI 14.700- 89.685) ($_{\text{nominal}}$p =0.0144), supporting the benefit of the treatment. Considering that the baseline level of fasting TG in patients enrolled in the Balance study was more than 2000 mg/dL, the overall population is considered at high risk of acute pancreatitis regardless of prior history of acute

pancreatitis. The CHMP considers that the indication of olezarsen for a broad patients' population regardless of prior history of acute pancreatitis is justified.

It is considered that the reduction in the rate of acute pancreatitis is clinically relevant. Long-term efficacy data on olezarsen treatment has been provided up to 3 years demonstrating that the achieved decrease in TG during the first 6 months of treatment could be maintained.

Efficacy data are based on a single pivotal placebo-controlled trial. An update on efficacy and safety data from the open-label extension study ISIS 678354 CS13 as well as Study ISIS 678354-CS7, in which patients with FCS previously treated with volanesorsen, was submitted by the applicant. The data provided for patients treated up to 2.5 years in ISIS 678354-CS13 and up to 3 years in ISIS 678354-CS7 show sustained decrease in fasting TG and apoC-III levels from baseline. Some fluctuations in fasting TG and apoC-III should be expected during the treatment of patients, but a long-term decrease in fasting TG and apoC-III levels has been observed on treatment with olezarsen.

3.4. Unfavourable effects

In Pool 4 (including all FCS population studies (CS3 + CS13 + CS7)), AEs were reported in 58 (87.9%) patients in olezarsen 80 mg group, compared with 22 (95.7%) patients in the placebo group. Related AEs (ADRs) were reported in 31 (47.0%) patients in the olezarsen 80 mg group, compared with 5 (21.7%) patients in the placebo group. SAEs were detected in 11 (16.7%) patients in the olezarsen 80 mg group, compared with 9 (39.1%) patients in the placebo group.

AESI 2 is considered as key unfavourable effect after assessment of the results of the olezarsen clinical trials. AESI 2 is defined as requirement of any use of medications (prophylactic treatment, such as antihistamines, acetaminophen, non-steroidal anti-inflammatory drugs, corticosteroids, etc.) as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction. In Pool 4 (CS13 in specific), 1 (1.5%) patient in the olezarsen 80 mg group experienced anaphylactic reaction which was assessed as serious and related to study treatment. No AESI 2 occurred in any other group across olezarsen clinical trials.

In Pool 4, 11 (16.7%) patients in the olezarsen 80 mg group experienced an ISR compared with 2 (8.7%) in the placebo group.

In Pool 4, a platelet count decrease (platelet level of 100,000/mm^3 to < 140,000/mm^3) occurred in 25 (37.9 %) patients in olezarsen 80 mg group, compared with 3 (13.0%) in the placebo group. A single occurence of ≥ 30% decrease from baseline occurred in 35 (53.0%) patients in the olezarsen 80 mg group, compared with 7 (30.4%) in the placebo group.

In Pool 4, 2 (3.0%) patients in the olezarsen 80 mg group experienced hypersensitivity, compared with none in the placebo group.

3.5. Uncertainties and limitations about unfavourable effects

The pooled, safety population in clinical trials with FCS patients is quite small, which may limit the detection of less frequent and potentially serious AEs.

Data on long-term safety is limited. Although most of AEs, recognized as class AEs, did not occur more often in olezarsen 80 mg group, compared with placebo, it is unclear if it would still be the case after long-term treatment with olezarsen.

In the active treatment group, a slightly higher rate of discontinuation (with consequent lower exposure) was observed compared with the placebo group. The AEs most related to the discontinuation were about General disorders (in particular: administration site AEs) and Gastrointestinal disorders.

Slight fluctuations in the platelet count were observed in the FCS population, however, platelet count decreases in olezarsen-treated patients were not clinically meaningful and did not warrant a warning on platelet monitoring. It is important to note though that patients with a platelet count < 100,000 mm^3 were excluded from clinical trials, thus the safety of olezarsen in regard to platelet count on this population is unknown. No drug-drug interaction with other medicines has been studied that can have an impact on platelet count or function.

In the study CS8, ALT and AST showed small increases in mean percent change from baseline over time in both olezarsen arms, compared to placebo. These increases remained within the normal range, thus it is not clear what impact can the IMP have on the liver safety, since data in subjects with liver impairment/disease are limited.

3.6. Effects table

Table 96. Effects Table for Tryngolza for Familial Chylomicronemia Syndrome (primary analysis).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Decrease in fasting TG level at Month 6	Percent change in fasting TG from Baseline at Month 6 (average of Weeks 23, 25, and 27) compared with placebo	mg/dL; % LSM	-43.50% (95% CI -69.085, -17.921)	-	p=0.0009 Uncertainties: pre-defined TG level of < 500 - 880 mg/dL was not reached in the majority of patients Based on one single pivotal study.	ISIS 678354-CS3
Adjudicated acute pancreatitis event rate from week 1 to week 53	Mean event rate/100 patient year	-	4.37 (95% CI 0.942-20.298)	36.31 (95% CI 14.700, 89.685)	Mean rate ratio olezarsen-placebo: 0.12 (95% CII 0.022, 0.656) $_{nominal}$p=0.0144	ISIS 678354-CS3 *Ad hoc*
Unfavourable Effects						
Hypersensitivity FMQ (Narrow)	Incidence Anaphylactic reaction Hypersensitivity	%	 1.5 3,0	 0 0		1
ISR	Incidence	%	16.7	8.7	Similar pattern noticed across all 5 pools	1
Platelet count decrease	Incidence Platelet count decrease	%	 37.9	 13.0	Similar pattern noticed across all 5 pools There is very limited	1

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	100,000/mm^3 to < 140,000/mm^3 Single occurence of ≥ 30% decrease from baseline		53.0	30.4	data on patients with platelet count < 100,000 m^3	

Notes: 1 – data from SCS, Pool 4, 80 mg olezarsen group

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

FCS treatment aims at preventing the risk of pancreatitis by lowering triglycerides, if feasible below the threshold of < 500 mg/dL (Sniderman AM, 2012) or < 880 mg/dL (ESC/EAS Guidelines, 2019).

The efficacy and safety of olezarsen 80 mg was demonstrated in adults with genetically confirmed familial chylomicronemia syndrome (FCS). Treatment with olezarsen sodium (Tryngolza) administered subcutaneously in patients with genetically confirmed FCS resulted in a statistically significant decrease in fasting TG level and a significantly lower number of adjudicated acute pancreatitis events after one year treatment compared with placebo. Overall, the efficacy data obtained in the pivotal study showed a statistically significant decrease in fasting TG level from baseline to Month 6 in patients treated with 80 mg of olezarsen compared with placebo (43.3%), which was maintained and even increased at Month 12 (59.4%). This effect was due to a significant lowering of apoC-III levels of approximately 75% to 5 mg/ml. The decrease in fasting TG levels resulted in a reduction in the rate of acute pancreatitis (AP).

Despite the fact that the vast majority of patients treated with olezarsen did not decrease TG below the threshold of 500 - 880 mg/dL – meaning they were still at high risk of pancreatitis - the mean event rate of acute pancreatitis event in the pooled olezarsen group (80 mg +50 mg) was significantly lower compared with the placebo group. Moreover, the provided clinical data demonstrate that the treatment of patients with FCS with olezarsen 80 mg much is safer and has an easier dosing frequency than existing alternatives (every 4 weeks vs. every week) in particular in regard to platelet count abnormalities and severe clinical bleeding events. Consequently, olezarsen 80 mg could be used in previously excluded sub-groups of patients with platelet count platelet count from < 140 × 10^9/L to < 100 × 10^9/L (volanesorsen is contraindicated to be used in this patient population due to significant safety concerns). For these patients there is currently no alternative as volanesorsen is contra-indicated.

Overall, the frequency of AEs was similar between olezarsen and placebo. With regard to safety, AE of special interest 2 (AESI 2), defined as requirement of any use of medications (prophylactic treatment, such as antihistamines, acetaminophen, non-steroidal anti-inflammatory drugs, corticosteroids, etc.) as pre-treatment to avoid a hypersensitivity reaction or recurrence of a previous hypersensitivity reaction, is considered as key unfavourable effect after assessment of the results of the olezarsen

clinical trials. Since the mean exposure duration was slightly less than one year, long term safety is not well characterized. In particular CV safety should be further monitored. Balance of benefits and risks

Treatment with olezarsen sodium (Tryngolza) administered subcutaneously in patients with Familial Chylomicronemia Syndrome resulted in statistically significant decrease in fasting TG level and a lower number of adjudicated acute pancreatitis events for one year treatment compared with placebo. Overall, the efficacy data obtained in the pivotal study showed a statistically significant decrease in fasting TG level from baseline to Month 6 in patients treated with 80 mg olezarsen compared with placebo (43.3%), which was maintained and even increased at Month 12 (59.4%). The decrease in fasting TG levels resulted in a reduction in the rate of acute pancreatitis (AP) within a limited treatment timeframe. The provided clinical data demonstrate that treatment of patients with FCS with olezarsen 80 mg is safer and easier to use than existing alternatives (dosing frequencies every 4 weeks vs. every week and no platelet count abnormalities). Olezarsen 80 mg can be used in previously excluded sub-groups of patients treated with volanesorsen– patients with platelet count platelet count from < 140 × 10^9/L to < 100 × 10^9/L (volanesorsen is contraindicated to be used in this patient population due to significant safety concerns).

Following the recommendation of CHMP in the previous round of the assessment, the applicant agreed to modifying the indication statement as follows:

"Tryngolza is indicated as an adjunct to diet in adult patients for treatment of genetically confirmed familial chylomicronemia syndrome (FCS)." The Product Information (PI) and RMP have been revised accordingly.

3.7.2. Additional considerations on the benefit-risk balance

Updated clinical efficacy data from the open-label extension study and open-label safety study of AKCEA-APOCIII-LRXa, administered subcutaneously to patients with FCS previously treated with volanesorsen would be desirable to substantiate the benefit/risk evaluation.

3.8. Conclusions

The overall benefit/risk balance of Tryngolza is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tryngolza is similar to Waylivra within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Derogation(s) from market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogation laid down in Article 8.3 of the same Regulation applies:

- the applicant could establish in the application that the medicinal product, although similar to Waylivra, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication (see Appendix on derogations).

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tryngolza is favourable in the following indication(s):

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that olezarsen in comparison to volanesorsen previously authorised as a medicinal product in the European Union is to be qualified as a new active substance as it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.