▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tryngolza 80 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose pre-filled pen contains 80 mg olezarsen (as olezarsen sodium) in 0.8 mL solution.

Each mL contains 100 mg olezarsen (as olezarsen sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution with a pH of approximately 7.4 and osmolality of approximately 290 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Tryngolza is indicated as an adjunct to diet, in combination with other lipid-lowering therapies, for the treatment of adult patients with severe hypertriglyceridaemia (sHTG, fasting triglyceride levels of ≥ 880 mg/dL [≥ 10 mmol/L]).

4.2 Posology and method of administration

Posology

The recommended dose of olezarsen is 80 mg administered by subcutaneous injection once monthly.

Missed dose
If a dose is missed, Tryngolza should be administered as soon as possible. Dosing at monthly intervals should be resumed from the date of the most recently administered dose.

Special populations

Elderly population
No dose adjustment is required in patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 90 mL/min/1.73 m^2) (see section 5.2).

Olezarsen has not been studied in patients with severe renal impairment or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the risk.

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] with aspartate aminotransferase [AST] > ULN, or total bilirubin > 1-1.5 × ULN with any AST) (see section 5.2).

Olezarsen has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the risk.

Paediatric population
The safety and efficacy of this medicinal product in children and adolescents below 18 years of age have not yet been established. No data are available (see section 5.1).

Method of administration

This medicinal product is intended for subcutaneous use only. It should not be administered intramuscularly.

Each pre-filled pen is for single use only.

Patients and/or caregivers should be trained in the administration of this medicinal product in accordance with the comprehensive instructions for use provided at the end of the package leaflet.

This medicinal product should be administered into the abdomen or front of the thigh. The back of the upper arm can also be used as an injection site if a healthcare provider or caregiver administers the injection. It should not be injected into skin that is bruised, tender, red, or hard, into scars or damaged skin; the area around the navel should be avoided.

Some patients with FCS 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.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions (including symptoms of diffuse erythema and chills) have been reported in patients treated with Tryngolza (see section 4.8). If a serious hypersensitivity reaction occurs, Tryngolza must be discontinued immediately and appropriate therapy initiated.

General

Based on current available safety data for olezarsen in patients with FCS or sHTG, no serious risks of thrombocytopenia, hepatotoxicity, or renal toxicity were identified during clinical development; these

adverse reactions have been observed with some antisense oligonucleotides and cannot be completely excluded.

LDL-C

Treatment with olezarsen may increase low-density lipoprotein cholesterol (LDL-C) levels. In clinical studies, the LDL-C increased but remained within the normal range. The effect of olezarsen on cardiovascular risk is currently unknown. LDL-C should be monitored during treatment with olezarsen.

Use in patients with low platelet counts

Some patients with FCS or sHTG are susceptible to platelet count variability over time as part of the natural history and progression of the disease. There are limited data available on the use of olezarsen patients with platelet count < 100 000/mm^3.

Excipient with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In vitro studies show that olezarsen is not a substrate or inhibitor of transporters, does not interact with highly plasma protein bound medicines, and is not an inhibitor or inducer of cytochrome P450 (CYP) enzymes. Oligonucleotide therapeutics, including olezarsen, are not typically substrates of CYP enzymes. Therefore, olezarsen is not expected to cause or be affected by interactions mediated through transporters, plasma protein binding or CYP enzymes.

Tryngolza can be used with other lipid-lowering medicines, for example statins and fibrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of olezarsen in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Tryngolza during pregnancy and women of child-bearing potential should practice effective contraception.

Breast-feeding

There is no information on the excretion of olezarsen/metabolites in human milk, the effects of olezarsen on breastfed newborns/infants, or the effects of olezarsen on milk production in treated women (see section 5.3).

The unconjugated antisense oligonucleotide (ASO), which shares the same nucleotide sequence but lacks N-acetylgalactosamine (GalNAc), was present in the milk of lactating mice at very low levels. Oligonucleotide-based products typically have poor oral bioavailability. Due to the poor oral

bioavailability of this medicinal product, it is considered unlikely that low levels present in human milk will lead to clinically relevant levels in breastfed newborns/infants.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data on the effect of this medicinal product on human fertility are available.

No adverse effects of olezarsen on fertility were seen in mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Olezarsen has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In patients with FCS or sHTG, the most commonly reported adverse drug reactions during treatment with olezarsen were injection site reactions (17.9%), arthralgia (10.7%), headache (8.7%), vomiting (5.6%) and myalgia (5.4%).

Tabulated list of adverse reactions

The safety data described below reflects exposure to olezarsen in 89 patients with FCS and in 303 patients with sHTG (fasting triglyceride levels of ≥ 880 mg/dL [≥ 10 mmol/L]) in clinical trials who received at least one dose of olezarsen. Of these, 77 patients with FCS and 285 patients with sHTG received at least 6 months of treatment and 65 patients with FCS and 259 patients with sHTG received approximately 12 months of treatment. The mean duration of treatment for patients with FCS was 521 days (range: 28 to 1 080 days) and 342.6 days (range: 26 to 393 days) for patients with sHTG respectively.

Adverse reactions are listed according to MedDRA system organ class. The frequency of adverse reactions is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (frequency cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse reactions[1]

MedDRA System Organ Class **Adverse reaction**	**Frequency**
Immune system disorders	
Hypersensitivity	Uncommon
Nervous system disorders	
Headache	Common
Gastrointestinal disorders	
Vomiting	Common
Musculoskeletal and connective tissue disorders	
Arthralgia	Very common

MedDRA System Organ Class Adverse reaction	Frequency
Myalgia	Common
General disorders and administration site conditions	
Injection site reactions[2]	Very common
Chills	Common
Investigations	
Alanine aminotransferase increased	Common
Aspartate aminotransferase increased	Common

[1]Adverse reactions were reported in clinical studies that included patients receiving olezarsen 50 mg or 80 mg once monthly.
[2]See section "Description of selected adverse reactions" for details regarding injection site reactions.

Description of selected adverse reactions

Hypersensitivity
Hypersensitivity has been observed with olezarsen. Severe hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias) have been observed in 2 patients with FCS in clinical trials. In both patients the events were acute, required treatment, and resulted in treatment discontinuation.

Injection site reactions
Injection site reactions occurred in patients with FCS and in patients with sHTG treated with olezarsen. These local reactions consisted of injection site erythema (10.7%), pain (4.1%), discolouration (3.6%), pruritus (2.3%), rash (2.0%), and swelling (2.0%). These events were mostly mild and generally self-limiting or could usually be managed with symptomatic treatment.

Laboratory observations

Increase in hepatic transaminases
In phase 3 clinical studies, increases of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) mean values from baseline to month 6 were observed, but remained within the normal range and stabilised afterwards.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via;

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents, anatomical therapeutic chemical (ATC) code: C10AX21

Mechanism of action

Olezarsen is an antisense oligonucleotide-triantennary N-acetylgalactosamine ($GalNAc_3$) conjugate that causes degradation of apolipoprotein C3 (apoC-III) messenger ribonucleic acid (mRNA) through selective binding to its mRNA, which leads to ribonuclease H1 (RNase H1)-mediated cleavage of apoC-III mRNA. Olezarsen is perfectly complementary to the site on chromosome 11 positions 116, 833, 046 through 116, 833, 065, corresponding to the gene apoC-III according to Ensembl version 109 (GRCh38 build) of the *homo sapiens* genome. This results in specific reductions of serum apoC-III protein leading to plasma triglyceride reductions. Studies suggest that apoC-III regulates both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins.

Pharmacodynamic effects

Effects of olezarsen on lipid parameters in patients with FCS:
In the clinical trial in patients with FCS (Balance trial), administration of olezarsen decreased apoC-III, triglycerides (TG), chylomicron triglycerides, apolipoprotein B-48 (apoB-48), total cholesterol (TC), and non-high-density lipoprotein cholesterol (non-HDL-C). It also increased high-density lipoprotein cholesterol (HDL), total apolipoprotein B (apoB), and low-density lipoprotein cholesterol (LDL-C). Mean LDL-C levels remained within the normal range (i.e., < 70 mg/dL [< 1.8 mmol/L]) for 74% of patients.

Effects of olezarsen on lipid parameters in patients with sHTG:
In the clinical trials in patients with sHTG (CORE and CORE2 trials), administration of olezarsen decreased apoC-III, triglycerides, total cholesterol, remnant cholesterol, non-high-density lipoprotein cholesterol and apoB-48. Total apoB remained largely stable. Olezarsen also increased HDL-C and LDL-C. Mean LDL-C levels remained below 100 mg/dL (2.6 mmol/L) through the 12-month study period.

Cardio electrophysiology
At a dose 1.5-times the maximum recommended dose for olezarsen, no clinically significant corrected QT interval prolongation was observed.

Clinical efficacy and safety

Adult Patients with Familial Chylomicronemia Syndrome
The efficacy and safety of olezarsen were studied in a randomised, multicentre, double-blind, placebo-controlled clinical trial (Balance trial) that included 66 adult patients with FCS. Patients were screened and enrolled based on documented loss-of-function variants in various genes known to cause complete or partial deficiency in the function of lipoprotein lipase, an enzyme that hydrolyzes TGs transported by TG-rich lipoproteins into free fatty acids. After a ≥ 4-week run-in period where patients continued to follow a diet with ≤ 20 g fat per day, patients were randomly assigned 1:1 to cohort A (50 mg) or cohort B (80 mg) and each cohort was further randomised 2:1 to receive olezarsen or placebo, respectively, via subcutaneous injection over a 53-week treatment period.

The main inclusion criteria for the trial were: a diagnosis of FCS confirmed by documentation of homozygote, compound heterozygote, or double heterozygote for loss-of-function mutations in type 1-causing genes [such as Lipoprotein Lipase (LPL), Glycosylphosphatidylinositol Anchored

High Density Lipoprotein Binding Protein 1 (GPIHBP1), Apolipoprotein A5 (APOA5), Apolipoprotein C2 (APOC2), Glycerol-3-Phosphate Dehydrogenase 1 (GPD1), or Lipase Maturation Factor 1 (LMF1)]; and with or without a history of pancreatitis. History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalisation for severe abdominal pain consistent with acute pancreatitis with no alternate diagnosis, within 10 years prior to screening. Enrolment of patients without a history of pancreatitis was capped at 35% (i.e. ≤ 21 of the 60 planned patients).

Patient demographic and baseline characteristics were generally similar across the 3 treatment groups. A total of 66 patients were enrolled. The mean age was 45 years, 38 (58%) were females, 56 (85%) were white, and 59 (89%) of non-Hispanic or Latino ethnicity. Out of a total of 66 patients, 55 (83%) had loss of function mutation in LPL gene including 40 (61%) with homozygote LPL mutation, and 11 (17%) had other causative variants in APOA5, GPIHBP1, LMF1 and APOC2 genes. The proportion of patients with diabetes at enrolment was 32% in the olezarsen 80 mg group and 14% in the olezarsen 50 mg group compared with 26% in the placebo group. Across all treatment groups, patients enrolled were being treated with statins (24%), omega-3 fatty acids (38%), fibrates (46%), or other lipid-lowering therapies (9%) at trial entry. Patients on lipid-lowering therapy had to maintain stable doses for at least 4 weeks prior to screening and remain on stable therapy throughout the trial. Additionally, all patients were to adhere to their prescribed diet for the entire duration of the trial. Seventy-one percent (71%) of all patients had a history of documented acute pancreatitis in the prior 10 years. Mean (standard deviation [SD]) fasting TG level at baseline was 2 629.5 (1 315.45) mg/dL (29.7 [14.86] mmol/L).

Olezarsen led to a statistically significant reduction in triglyceride levels in the 80 mg group as compared to placebo at the primary efficacy endpoint, defined as percent change in fasting triglycerides from baseline to month 6 (average of weeks 23, 25, and 27), see Table 2 below. Olezarsen 50 mg is not an approved dosing regimen for FCS and further analyses are not shown.

Table 2: Mean baseline (BL) and least-squares mean percent (%) changes from baseline in lipid/ lipoprotein parameters in patients with FCS at months 6 and 12 (Balance trial)

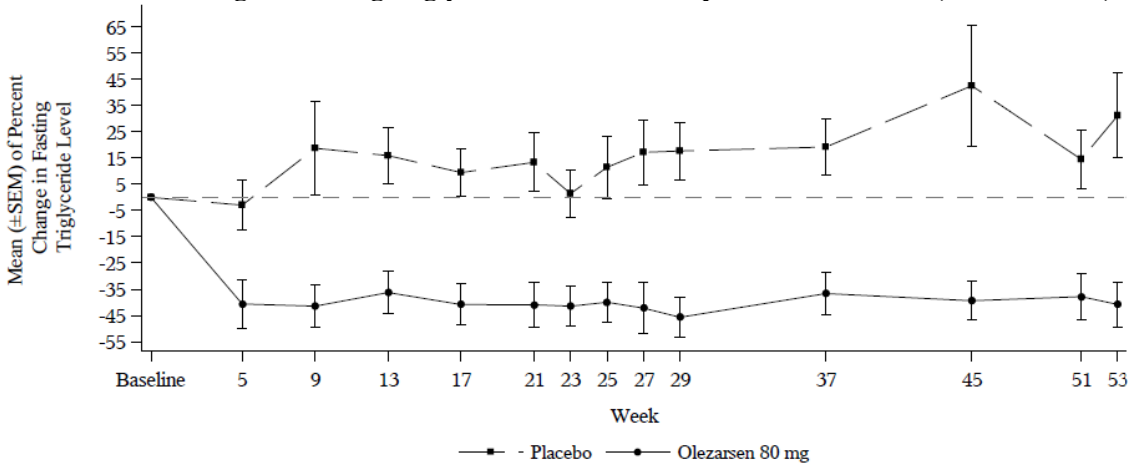
Parameter	**Olezarsen 80 mg N = 22**			**Placebo N = 23**			**Olezarsen 80 mg vs. Placebo**	
	BL	**% change month 6**	**% change month 12**	**BL**	**% change month 6**	**% change month 12**	**Treatment difference (95% CI)**	
							at month 6	**at month 12**
Triglycerides mg/dL (mmol/L)	2 613.1 (29.5)	-32	-39	2 595.7 (29.3)	+12	+21	-43.5* (-69.1, -17.9)	-59.4† (-90.7, -28.1)
ApoC-III mg/dL	27.5	-66	-64	27.7	+8	+17	-73.7† (-94.6, -52.8)	-81.3† (-104.7, -57.9)
ApoB-48 mg/dL	11.6	-59	-79	14.2	+25	-4	-84.0† (-137.0, -31.0)	-75.6 (-153.2, +1.9)
Non-HDL-C mg/dL (mmol/L)	262.9 (6.8)	-19	-28	271.3 (7.0)	+5	+12	-24.2† (-40.5, -7.9)	-39.7† (-63.1, -16.3)

Abbreviations: apoB-48 = apolipoprotein B-48; apoC-III = apolipoprotein C-III; non-HDL-C = non-high density lipoprotein cholesterol; N = number of patients; CI = confidence interval; BL = baseline.
Note: Analyses results were based on an analysis of covariance model with treatment, the two randomisation stratification factors, prior history of pancreatitis within 10 years prior to screening (yes vs. no), previous

treatment with the unconjugated ASO (yes vs. no) as the fixed effects and log-transformed baseline value as a covariate. Missing data was imputed using placebo washout imputation. The 95% CIs of treatment differences were calculated using a robust variance estimator.
* Reached statistical significance (p value < 0.05).
† Reached nominal significance (p value < 0.05).

The placebo adjusted percent change in TG levels from baseline at month 12 in the olezarsen 80 mg treated group was nominally significant (Table 2). Following administration of olezarsen 80 mg dose every 4 weeks, a decrease in fasting apoC-III was observed at the first assessment (week 5). The placebo-corrected, percent change from baseline was -57%, -69%, -74%, and -81% at months 1, 3, 6, and 12, respectively. Reductions in apoB-48 and non-HDL-C levels in the olezarsen 80 mg treated group were demonstrated at month 6 and were sustained at month 12. Mean percent changes in TG levels from baseline over time demonstrated a consistent lowering effect during the 12-month treatment period (Figure 1).

Figure 1: Percent change in fasting triglyceride over time in patients with FCS (Balance trial)



Placebo	23	23	21	21	22	22	19	21	19	21	22	20	19	20
Olezarsen 80 mg	22	21	20	21	20	20	15	19	16	20	18	19	15	17

Over the 12-month treatment period, the numerical incidence of pancreatitis in patients treated with olezarsen 80 mg was lower compared with placebo (1 patient experienced 1 event of adjudicated acute pancreatitis in the olezarsen 80 mg group compared with 11 events experienced by 7 patients in the placebo group). The time to first pancreatitis event was longer in the olezarsen 80 mg group (357 days) compared to placebo (9 days). The mean pancreatitis event rate per 100 patient years was 4.37 for the total olezarsen group (80 mg and 50 mg group) compared with 36.31 for the placebo group. The mean pancreatitis event rate ratio for total olezarsen to placebo was 0.12 (95% CI: 0.022, 0.656).

Adult patients with severe hypertriglyceridaemia
The efficacy and safety of olezarsen were studied in two randomised, double-blind, placebo-controlled clinical trials (CORE, and CORE2) with identical study design, that included 617 and 446 patients, respectively, with baseline fasting triglyceride levels ≥ 500 mg/dL (≥ 5.6 mmol/L) and on optimised, stable background lipid-lowering therapy prior to enrolment and throughout the trial. After an approximately 4- to 8-week screening and qualification period that included at least 2 weeks of diet and lifestyle stabilisation, patients were randomly assigned to receive subcutaneous injections once every 4 weeks of olezarsen 50 mg (n=354 in CORE and CORE2) or 80 mg (n=351), or placebo (n=358) for a 53-week treatment period.

Patients were stratified by baseline fasting triglyceride levels ≥ 880 mg/dL (≥ 10 mmol/L) or < 880 mg/dL (< 10 mmol/L). Overall, in CORE and CORE2, 150 patients on olezarsen 50 mg, 153 patients on olezarsen 80 mg, and 152 patients on placebo had baseline fasting triglyceride levels

≥ 880 mg/dL (≥ 10 mmol/L) (sHTG). In patients with sHTG (baseline triglyceride levels ≥ 880 mg/dL [≥ 10 mmol/L]), patient demographic and baseline characteristics across pooled CORE and CORE2 were generally similar across the 3 treatment groups. The majority of patients were male (approximately 80%) with a median age of 52 years; 12% were ≥ 65 years. Most patients were white (88%) and mildly obese (median BMI 31 kg/m²). Most patients used statins (about 70%) and/or fibrates (about 72%) at baseline and were allowed to maintain the use of these medicines in the trials (CORE, and CORE2). At enrolment 60.9% of patients had diabetes mellitus type 2; 98% of patients were on background lipid-lowering therapies and 25.7% of patients had a history of pancreatitis within the prior 10 years. At baseline, mean (SD) fasting triglyceride levels were 1 764.2 (1 237.57) mg/dL (19.9 [14.0] mmol/L) and median 1 379 mg/dL (15.6 mmol/L) (range min-max: 880-13 545 mg/dL [9.94-153.1 mmol/L]).

Olezarsen 80 mg led to a statistically significant reduction in triglyceride levels from Baseline to month 6 (average of Weeks 25 and 27) compared to placebo (primary endpoint) in both CORE and CORE2, see Table 3 below. Olezarsen 50 mg is not an approved dosing regimen for sHTG and further analyses are not shown.

Table 3: Mean baseline (BL) and least-squares mean percent (%) changes from baseline in lipid/lipoprotein parameters in patients with sHTG at months 6 and 12 (CORE and CORE2 trials)

Parameter	**Olezarsen 80 mg**			**Placebo**			**Olezarsen 80 mg vs. Placebo**	
	BL	**% change month 6[a]**	**% change month 12 [a]**	**BL**	**% change month 6[a]**	**% change month 12 [a]**	**Treatment difference [a] (95% CI)**	
							at month 6	**at month 12**
Individual study results								
CORE trial	N=96			N=95				
Triglycerides mg/dL (mmol/L)	1 797.9 (20.3)	-75	-73	1 890.6 (21.4)	-2	-9	-73.4* (-87.1, -59.7)	-63.8* (-78.1, -49.6)
CORE2 trial	N=57			N=57				
Triglycerides mg/dL (mmol/L)	1 827.9 (20.7)	-70	-64	1 658.3 (18.7)	-18	-8	-52.3* (-69.2, -35.4)	-56.1* (-76.2, -36.1)
Pooled CORE and CORE2	N=153			N=152				
ApoC-III mg/dL	46.9	-81	-79	46.7	-8	-9	-73.2* (-79.6, -66.8)	-70.2* (-77.0, -63.4)
Remnant cholesterol mg/dL (mmol/L)	192.6 (5.0)	-65	-58.0	182.7 (4.7)	-1	-1	-63.8* (-72.9, -54.8)	-57.0* (-68.3, -45.7)
Non-HDL-C mg/dL (mmol/L)	258.6 (6.7)	-42	-38	254.1 (6.6)	-7	-7	-35.3* (-41.7, -28.9)	-31.0* (-38.9, -23.2)

Abbreviations: apoC-III = apolipoprotein C-III; non-HDL-C = non-high density lipoprotein cholesterol; N = number of patients; CI = confidence interval; BL = baseline.
Note: Analyses results were based on an analysis of covariance. The model was fitted on % change from baseline to month 6/12 in Triglycerides. The model was fitted on % change from baseline to month 6/12 in fasting triglycerides as the dependent variable, with treatment group and the randomisation stratification factor prior history of pancreatitis within 10 years prior to screening as factors, and baseline fasting triglyceride value as a covariate. Missing data were multiply imputed.
[a] LS-Mean Estimate
[*] Reached statistical significance (p value < 0.0001)
Baseline was defined as the average of the pre-dose fasting measurement on Day 1 and all non-missing fasting measurements from the Qualification Period. If all measurements from Day 1 pre-dose and the Qualification Period were missing, then the last non-missing fasting measurement from the Screening Period was used instead.

The placebo adjusted percent change in TG levels from baseline at month 12 was statistically significant for the olezarsen 80 mg treated group in both CORE and CORE2 trials (Table 3). Olezarsen 80 mg led to statistically significant reductions in key lipid parameters (apoC-III, remnant cholesterol, non-HDL-C) compared to placebo at month 6 and sustained at month 12 in CORE and CORE2 trials (Table 3).

In CORE (Figure 2) and CORE2 (Figure 3), mean percent change from baseline in fasting triglycerides over time demonstrated a consistent triglyceride-lowering effect during the 12-month treatment period.

Figure 2. CORE: percent change in fasting triglycerides over time in patients with sHTG

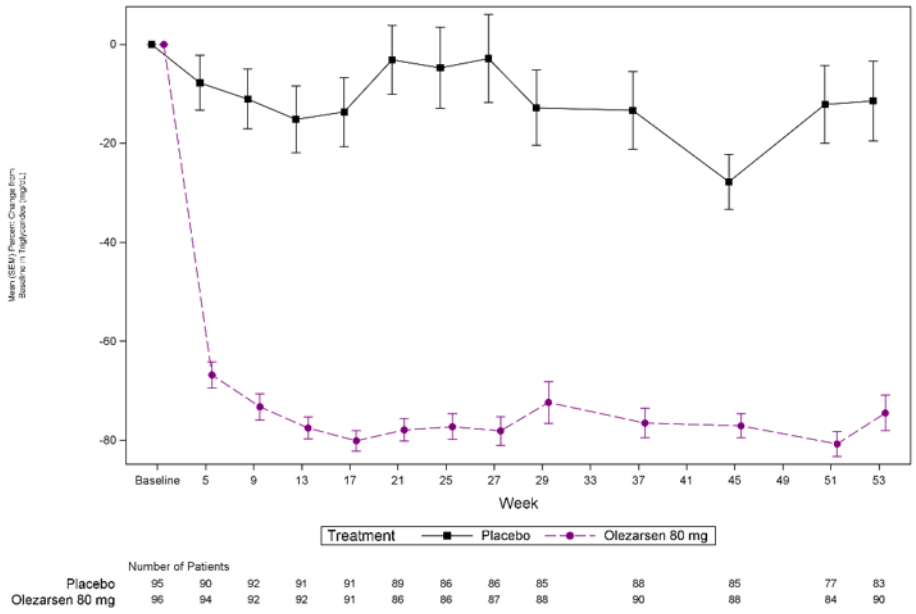
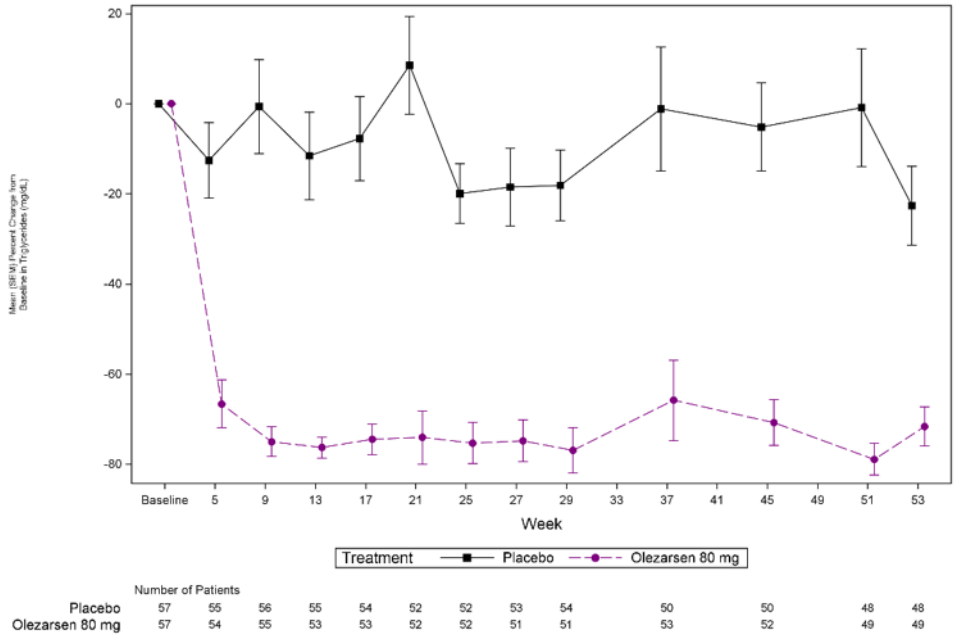


Figure 3. CORE2: percent change in fasting triglycerides over time in patients with sHTG



The proportions of patients who achieved the prespecified fasting triglyceride level of < 880 mg/dL (< 10 mmol/L) at month 12 were 81.7% (125/153) in the olezarsen 80 mg group (pooled across CORE and CORE2) and 39.5% (60/152) in the pooled placebo group (statistically significant odds ratio (95% CI) 9.78 [5.13, 18.67]).

Sixteen (16) patients (10.5%) in the pooled placebo group experienced 21 events of adjudicated acute pancreatitis, compared with 5 patients (1.7%) in the combined olezarsen group (olezarsen 80 mg and olezarsen 50 mg), who experienced 7 events.

For the combined olezarsen (50 mg and 80 mg) group, an 83% decrease in the mean adjudicated acute pancreatitis event rate (mean pancreatitis event rate ratio 0.17 [95% CI: 0.06, 0.45]) was observed compared with the pooled placebo group, a statistically significant reduction. A total of 9 patients needed to be treated with olezarsen to prevent 1 event of AP in 12 months.

Elderly population
In clinical trials, 111 (38%) patients with FCS and 56 (12.3%) patients with sHTG treated with olezarsen were ≥ 65 years of age. No overall differences in safety or efficacy were observed between these patients and younger adult patients.

Immunogenicity

Across the clinical trials in FCS (Balance), and in sHTG (CORE and CORE2), with duration of treatment up to 53 weeks, anti-drug antibodies (ADA) were very commonly detected, with 18 out of 43 (42%), 101 out of 197 (51%) and 55 out of 106 (52%) patients treated with olezarsen developing treatment-emergent ADAs, respectively. No evidence of ADA impact on pharmacodynamics, safety, or efficacy was observed.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with olezarsen in one or more subsets of the paediatric population in the treatment of FCS and has waived

the obligation to submit the results of studies with olezarsen in all subsets of the paediatric population in sHTG (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 or sHTG.

Olezarsen maximum concentration (C_{max}) and area under the curve (AUC) showed a slightly greater than dose-proportional increase following single subcutaneous doses ranging from 10 to 120 mg (i.e. 0.13- to 1.5-times the recommended dose) in healthy volunteers.

Post-hoc population estimates (geometric mean, geometric CV%) at steady state of C_{max}, and AUC over the dosing interval (AUC_{τ}) were 696 ng/mL (89.6 %) and 6 340 ng×h/mL (61.3 %), respectively, following 80 mg every 4 weeks in patients with FCS; 258 ng/mL (56.1 %) and 6 350 ng×h/mL (87.4 %), respectively, at 80 mg every 4 weeks in patients with sHTG. No accumulation of olezarsen C_{max} was observed.

Absorption

Following subcutaneous administration, olezarsen is rapidly absorbed with the time to maximum plasma concentration of approximately 2 hours post dose, based on population estimates.

Distribution

Olezarsen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing. Olezarsen is bound to human plasma proteins (> 99%) *in vitro*. The population estimates for the apparent central volume of distribution is 91.9 L and 127 L, and the apparent peripheral volume of distribution is 2 960 L and 6 660 L, for patients with FCS or sHTG ≥ 500 mg/dL (≥ 5.6 mmol/L), respectively.

Biotransformation

Olezarsen is not a substrate for CYP metabolism and is metabolised by endo- and exonucleases to short oligonucleotide fragments of varying sizes.

Elimination

The terminal elimination half-life is approximately 4 weeks.
The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose within 24 hours.

Immunogenicity

Observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay. The presence of ADAs did not affect olezarsen plasma C_{max} but increased trough concentrations (C_{trough}).

Special populations

Renal impairment
No formal clinical trials have been conducted to investigate the effect of renal impairment on olezarsen PK. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of olezarsen based on mild and moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73 m^2).

Olezarsen has not been studied in patients with severe renal impairment or end-stage renal disease.

Hepatic impairment
No formal clinical trials have been conducted to investigate the effect of hepatic impairment on olezarsen PK. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of olezarsen based on mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN; or total bilirubin > 1-1.5× ULN with any AST).

Olezarsen has not been studied in patients with moderate or severe hepatic impairment.

Age, gender, weight and race
Based on the population pharmacokinetic and pharmacodynamic analysis, body weight (ranging from 45 to 166 kg), gender, and race have no clinically meaningful effect on olezarsen exposure or apoC-III and triglyceride reductions at steady-state following 80 mg olezarsen every 4 weeks.

No overall differences in pharmacokinetics were observed between adult and elderly patients (age ≥ 65 years).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In animal studies of the unconjugated form of olezarsen, volanesorsen, available data have shown excretion of very low amounts of volanesorsen in milk. Owing to poor oral bioavailability of volanesorsen, it is considered unlikely that these low milk concentrations would result in systemic exposure from nursing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Store in the original package in order to protect from light.

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.

6.5 Nature and contents of container

0.8 mL solution for injection 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.

Pack size of one pre-filled pen.

6.6 Special precautions for disposal and other handling

The single dose pre-filled pen should be removed from a refrigerator (2 °C to 8 °C) at least 30 minutes before use to allow it to reach room temperature (up to 30 °C) prior to injection. Other warming methods (e.g. hot water or microwave) should not be used.

The medicinal product should be inspected visually prior to administration. The solution should be a clear and colourless to yellow liquid. It is normal to see air bubbles in the solution. If the solution is cloudy or contains visible particulate matter, the content must not be injected and the medicinal product should be returned to the pharmacy. Do not use if the solution appears frozen.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.