IONIS IRELAND LIMITED

EU RISK MANAGEMENT PLAN (EU RMP) FOR TRYNGOLZA (OLEZARSEN)

Version: 0.5

Data Lock Point: 01 Dec 2023

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RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: Update to the RMP as part of the response to Day 195 Questions EMA/CHMP/170347/2025

Summary of significant changes in this RMP:

Reference to specific adverse drug reaction follow-up forms have been removed from Section III.1 and Annex 4.

Summary RMP section II.B was updated to include Summary of Important Risks table.

Section SVII 1.2: Missing information – Long Term Safety section was updated to remove: hepatotoxicity, renal toxicity and thrombocytopenia.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Special term	Definition/Explanation
2′-MOE	2′-*O*-methoxyethyl
AE	adverse event
ALT	alanine aminotransferase
apoC-III	apolipoprotein C-III
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under curve
C_{max}	maximum serum concentration
CNS	central nervous system
eGFR	estimated glomerular filtration rate
EEA	European Economic Area
EFD	embryo fetal development
EPAR	European Public Assessment Report
EU	European Union
FCS	familial chylomicronemia syndrome
FEED	fertility and early embryonic development
GalNAc	*N*-acetyl galactosamine
hERG	human Ether-à-go-go-related gene
HIV	human immunodeficiency virus
HTG	hypertriglyceridemia
IM	Immunogenicity
ISR	Injection site reactions
LICA	ligand-conjugated antisense oligonucleotide
LPL	lipoprotein lipase
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NOAEL	no observed adverse effect level
NORD	National Organisation for Rare Disorders

Abbreviation/Special term	Definition/Explanation
PK	pharmacokinetic
PLT	platelet
RMP	risk management plan
sHTG	severe hypertriglyceridemia
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
TEAE	treatment-emergent adverse event
TG	triglycerides
ULN	upper limit of normal

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	Olezarsen
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	Ionis Ireland Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	TRYNGOLZA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Antisense oligonucleotide (ASO)
	Summary of mode of action: Olezarsen is an antisense oligonucleotide-triantennary *N*-acetylgalactosamine ($GalNAc_3$) conjugate that causes degradation of *APOC3* mRNA through selective binding to its mRNA, which leads to RNase-H1-mediated cleavage of *APOC3* mRNA. This results in a reduction 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.
	Important information about its composition: Olezarsen is a 2′-*O*-methoxyethyl (MOE) chimeric ASO covalently bound to $GalNAc_3$, a high affinity ligand for the hepatocyte-specific asialoglycoprotein receptor. The purpose of the GalNAc conjugation is to improve the targeted delivery of the ASO to the target cell type, hepatocytes, and achieve pharmacologic activity at much lower doses.
Hyperlink to the Product Information	Proposed TRYNGOLZA Summary of Product Characteristics

Table 1: Product Overview (Continued)

Indication(s) in the EEA	Current: TRYNGOLZA (olezarsen) is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dosage of TRYNGOLZA is 80 mg administered by subcutaneous injection once monthly.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Not applicable
	Proposed: Injection: 80 mg/0.8 mL of olezarsen as a clear, colourless to yellow solution in a single dose pre-filled pen. Each single dose pre-filled pen contains 80 mg olezarsen (equivalent to 84 mg of olezarsen sodium) in 0.8 mL of solution.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the indication and target population

Familial chylomicronaemia syndrome

FCS is a rare, serious autosomal recessive inherited disease of lipid metabolism characterized by severely impaired lipoprotein lipase (LPL) function, resulting in decreased clearance of triglyceride-rich lipoproteins from plasma, causing severe hypertriglyceridemia and hyperchylomicronaemia. Patients with FCS have triglyceride (TG) levels approximately 10 to 100 times above the reference level of < 150 mg/dL (1.7 mmol/L) (Witztum *et al.* 2019).

Incidence

Although FCS may be diagnosed at any age, population-based studies on the global incidence of FCS are lacking. The incidence may be as high as 100 per million in certain populations, such as French Canadians or South Afrikaners, with the "founders effect" (a phenomenon where a small, isolated population of settlers or founders with a particular genetic trait expands over several generations, reducing genetic diversity within that population and resulting in a high incidence or prevalence of a particular genetic trait) (Falko 2018; NORD 2023).

Prevalence

Due to the rarity of FCS, determining its precise prevalence is challenging. However, there is a general consensus that the overall prevalence is likely to be 1-2 per million, corresponding to 0.01-0.02 per 10,000 (Brunzell 1999; Gotoda *et al.* 2012; NIHR 2013). Data on the prevalence of FCS in Europe is limited. According to a systematic survey of the literature on rare diseases, the Orphanet Rare Disease collection estimates that the prevalence of FCS ranges from 1 per 100,000 to 1 per 1,000,000 in Europe (Orphanet 2023)

In the Netherlands, investigators used information on patients with lipoprotein lipase (LPL) deficiency, which accounts for most documented FCS cases, to estimate a prevalence of approximately 2 per 1,000,000 (Nierman *et al.* 2005).

In Hungary, medical records from two major hospitals were analyzed using machine learning models. Out of 1,342,124 patients, 26 were identified with FCS, corresponding to a prevalence of 19.4 per 1,000,000 or 0.19 per 10,000 (Németh *et al.* 2022). Similarly, a review of 143,615 medical records from Niguarda Hospital in Italy, spanning from January 2016 to December 2018, identified 5 genetically confirmed FCS patients. This gives an estimated prevalence of 0.6 per 10,000, or 0.006% (Pavanello *et al.* 2022).

Evidence from non-EU countries supports these estimates. In the United States, a retrospective review of 1,627,763 patients in Maryland between 2013 and 2017 found a prevalence of 0.13 per 10,000 (Pallazola *et al.* 2020). In North Texas, a study identified 334 patients with FCS between 2015 and 2016, corresponding to a prevalence of 0.81 per 10,000, or 1 in 12,413) (Rengarajan *et al.* 2018). These estimates are consistent with those from Hungary and Italy (Németh *et al.* 2022; Pavanello *et al.* 2022).

Other U.S. studies reported prevalence estimates of 0.046 per 10,000 (Khavandi *et al.* 2018), 0.007 per 10,000 (Tripathi *et al.* 2021), and 1–2 per 1,000,000 (Warden *et al.* 2020). In French Quebec, Canada, the prevalence was estimated at 1 per 5,000, largely due to a founder effect

(Nierman *et al.* 2005; NORD 2023). Prevalence estimates from other countries are as follows: in England and Wales, an estimated 3,000 people have FCS (NIHR 2013); in Japan, 1–2 per 1,000,000 (Gotoda *et al.* 2012).

A summary of the references supporting the prevalence of FCS is provided in Table 2.

Table 2: Prevalence of Familial Chylomicronemia Syndrome

Region/ Country (State/City)	Estimated Prevalence	Reference
Global	1 per 1,000,000	(Brunzell 1999)
Europe and North America	1 per 300,000 (range: 1/100,000 to 1/1,000,000)	(Orphanet 2023)
Europe	1 to 2:1,000,000	(Nierman *et al.* 2005; Orphanet 2023)
Hungary	19.4 per 1,000,000	(Németh *et al.* 2022)
Italy	0.6 per 10,000 (0.006%)	(Pavanello *et al.* 2022)
The Netherlands	2 per 1,000,000	(Nierman *et al.* 2005)
United Kingdom	1 per 1,000,000	(NIHR 2013)
United States (Maryland)	~13 per 1,000,000	(Pallazola *et al.* 2020; Warden *et al.* 2020)
United States (North Texas)	0.18 per 10,000 (1 in 12,413)	(Rengarajan *et al.* 2018)
United States (New York)	0.046 per 10,000	(Khavandi *et al.* 2018)
United States (Southern California)	0.0026 to 0.007 per 10,000	(Tripathi *et al.* 2021)
United States (Oregon)	~1–2 per 1,000,000	(NIHR 2013)
United States (Southern California)	0.26 to 0.66 per 1,000,000	(Tripathi *et al.* 2021)
Canada (Quebec)	1 per 5,000	(Nierman *et al.* 2005)
Japan	1 to 2:1,000,000	(Gotoda *et al.* 2012)

Demographics of the Target Population – Age, Sex, Race/Ethnic Origin

Diagnosis of FCS

The diagnosis of FCS can be confirmed through genetic testing for mutations in the LPL gene or other genes essential for LPL function (Baass *et al.* 2020; Brown *et al.* 2020; Stroes *et al.* 2017). However, practical barriers such as inaccessibility, high costs, the challenge of interpreting inconclusive genetic results, and the potential for missing specific pathogenic variants due to ongoing updates in our understanding of pathogenicity limits the use of genetic testing for FCS confirmation (Baass *et al.* 2020; Brown *et al.* 2020; D'Erasmo *et al.* 2019; Moulin *et al.* 2018; Stroes *et al.* 2017). Owing to these limitations, employing a clinical diagnosis approach with a pragmatic scoring tool based on clinical signs and symptoms is recommended (Moulin *et al.* 2018).

An FCS diagnosis should be considered in patients with persistently elevated triglyceride (TG) levels (> 880 mg/dL), hypertriglyceridemia that is resistant to treatment, a history of pancreatitis, unexplained recurrent abdominal pain, low levels of low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C), and a reduced body mass index (BMI). The pragmatic diagnostic score for FCS proposed by Moulin et al. (Moulin *et al.* 2018) incorporates eight biological or clinical signs, such as the history of plasma TG levels, absence of secondary factors (excluding pregnancy and estrogenic oral contraceptives), history of acute pancreatitis, no history of familial combined hyperlipidemia, and the age at first symptom onset, to identify potential FCS patients when genetic testing is unavailable (Hegele *et al.* 2019; Moulin *et al.* 2018; O'Dea *et al.* 2019).

Risk Factors

FCS is primarily caused by genes encoding for LPL or its cofactors. Five (5) genes (LPL, LMF1, GPIHBP1, APOC2, APOA5) have been identified as the causative genes of monogenic chylomicronemia. Mutations in LPL account for more than 90% of monogenic chylomicronaemia cases. All of these genes are required for the normal function of LPL (Brahm & Hegele 2015). Derangement in gene products can directly or indirectly affect LPL function, leading to increased fasting plasma TG (Lewis *et al.* 2015). Homozygous, compound, or double heterozygous loss-of-function mutations of the LPL pathway genes usually result in monogenic chylomicronemia with an autosomal recessive mode of inheritance (Hegele *et al.* 2018). Heterozygous mutations or pathological variants in HTG-susceptible genes, including those for hepatic lipase (HL) and apolipoprotein E, may also predispose to chylomicronemia (Brahm & Hegele 2015; Hegele *et al.* 2014).

Loss-of-function mutations in LPL-pathway genes have been identified in less than 30% to 40% of patients suspected of monogenic chylomicronemia (Rabacchi *et al.* 2015; Surendran *et al.* 2012).

Main Treatment Options

Currently, volanesorsen (WAYLIVRA®) is the only therapeutic agent that has been approved specifically to treat FCS at this time. Standard therapeutic TG-lowering agents are largely ineffective in this population (Brahm & Hegele 2015; Stroes *et al.* 2017).

Treatment options for managing FCS symptoms are focused on restriction of dietary consumption of all fat and simple carbohydrates, control of secondary factors such as abstinence

from alcohol, use of lipid lowering pharmacologic therapies, which have been proven to be only minimally effective in this population, and the avoidance of drugs known to raise TG levels such as thiazides, beta-blockers, protease inhibitors, antipsychotics, antidepressants, and estrogen, (Brunzell 1995; Goldberg & Chait 2020; Valdivielso *et al.* 2014). Conventional lipid-lowering therapies such as fish oil, fibrates, and niacin are not very effective in the FCS population because they reduce plasma TG levels by decreasing the hepatic output of very low-density lipoproteins (VLDL) and/or by improving LPL activity (Brahm & Hegele 2015; Stroes *et al.* 2017). The goal of dietary therapy is to reduce plasma TG in the form of chylomicrons; to achieve this, patients must restrict their total fat intake (e.g., saturated, mono, or polyunsaturated) to less than 10–15% of caloric intake or 10–20 g per day (Valdivielso *et al.* 2014), the equivalent of approximately 1 tablespoon of olive oil. Compliance with such extreme restrictions at every meal throughout a lifetime is unsustainable, and such strict compliance does not eliminate the risk of complications, including acute pancreatitis (Češka *et al.* 2016; Stolte *et al.* 2021).

Volanesorsen is approved in the European Union, Great Britain, Brazil, and Chile, and is indicated as an adjunct to diet in adult patients with genetically confirmed FCS and at high-risk for pancreatitis, in whom response to diet and TG lowering therapy has been inadequate.

The safety profile of volanesorsen has been well defined. The risk of thrombocytopenia requires regular platelet level monitoring. Renal toxicity has also been observed, and injection site reactions have resulted in drug discontinuations (Waylivra-SmPC 2022; Witztum *et al.* 2019; 2023).

Better disease management approaches are therefore required for patients with FCS to reduce the risk of pancreatitis attacks and other consequences of prolonged chylomicronemia.

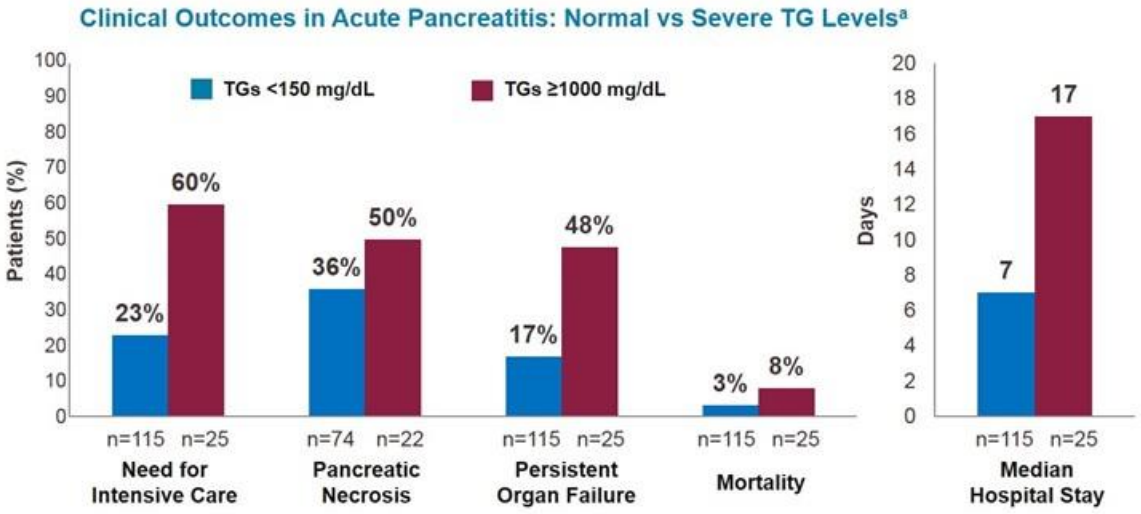
Natural history of the indicated condition in the untreated population, including mortality and morbidity and co-morbid conditions:

Chylomicrons are large (approximately 1 micron in diameter) lipoprotein particles that, if elevated, can result in clinically significant manifestations, including reduction of blood flow through the pancreatic microcirculation, leading to severe abdominal pain and pancreatitis (Valdivielso *et al.* 2014). Chylomicronaemia is a significant risk factor for acute pancreatitis, which can be fatal or lead to pancreatic damage, resulting in permanent exocrine or endocrine insufficiency in addition to other symptoms and complications (Symersky *et al.* 2006). If left untreated, patients with FCS may experience several severe and potentially life-threatening complications associated with the disease. Approximately 65-80% of patients with FCS will experience acute pancreatitis (Gaudet *et al.* 2016). One (1) study observed a significantly higher number of acute pancreatitis episodes experienced by patients with FCS within the preceding year, and over 70% of patients experience 10 or more episodes over the course of a lifetime (Davidson *et al.* 2018).

If FCS is left untreated, long-term complications may include chronic pancreatitis, pancreatogenic (type 3c) diabetes and endocrine and exocrine pancreatic insufficiencies, leading to digestive issues, steatorrhea, and diabetes (Symersky *et al.* 2006). Pancreatitis due to severe hypertriglyceridemia (sHTG) may be more severe with worse outcomes than pancreatitis of other aetiologies. One (1) study found that acute pancreatitis in patients with sHTG compared to those with normal TG levels (< 150 mg/dL) resulted in longer median hospital stays (17d vs. 7d), increased need for intensive care (60% vs. 23%), a higher rate of pancreatic necrosis

(50% vs. 36%), and more frequent persistent (i.e., > 48 hr) organ failure (48% vs. 17%) (Figure 1) (Nawaz *et al.* 2015). Further, persistent organ failure within the first week of severe acute pancreatitis has been associated with a higher mortality rate (Johnson & Abu-Hilal 2004). Patients with high TG and minimal LPL activity (i.e., FCS patients) may also be at enhanced risk of pancreatitis compared with patients with moderate HTG, and certainly in comparison with patients with normal TG levels. One (1) study demonstrated that FCS patients had a 360-fold greater risk of acute pancreatitis than in normotriglyceridemic individuals, and a 16-fold increase risk compared to patients with moderate hypertriglyceridemia (443 to ~800 mg/dL), underscoring the need to reduce TG in this population (Figure 2) (Gaudet *et al.* 2010).

Figure 1: Clinical Outcomes in Acute Pancreatitis

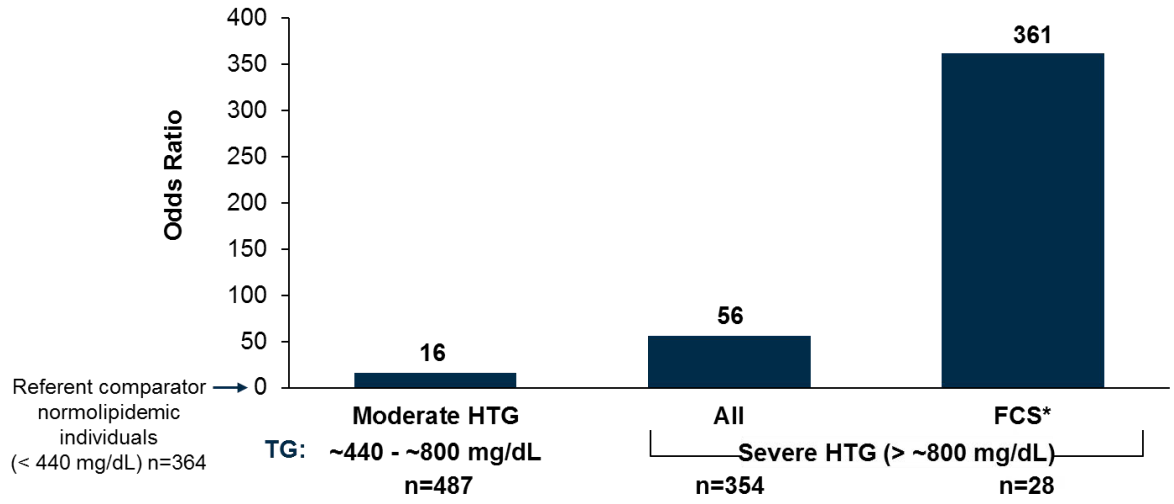


Adapted from Nawaz, *Am J Gastroenterol*, 2015.

[a] Patients were neither evaluated or diagnosed with FCS

Abbreviation: TG, triglyceride.

Figure 2: Risk of Acute Pancreatitis Associated with Moderate and Severe Hypertriglyceridaemia Compared to Normolipidemic Controls



Abbreviations: HTG = hypertriglyceridaemia.
Figures adapted from (Gaudet *et al.* 2010)

Across all etiologies, acute pancreatitis accounts for more than 220,000 hospital admissions in the United States each year. Overall, about 20% (44,000) of patients have a severe course, and 10 to 30% of those with severe acute pancreatitis die, which translates to a mortality rate of 2 to 6% across all causes (Whitcomb 2006). Across 17 countries in Europe, the incidence of acute pancreatitis ranged from 4.6 to 100 per 100,000 population, with the percentage change in incidence increasing over time (Roberts *et al.* 2017). Global estimates of incidence and mortality for acute pancreatitis were 33.74 cases per 100 000 person-years and 1.60 deaths per 100.000 person-years (Xiao *et al.* 2016).

Despite the great advances in critical care medicine over the past 20 years, the mortality rate of acute pancreatitis has remained slightly higher than 10% (Foundation 2024). While gallstones and alcoholism remain the most common cause of acute pancreatitis in the general population, it is estimated that up to 10% of acute pancreatitis is due to sHTG (Valdivielso *et al.* 2014).

Persistently elevated TG, nearly always exceeding 1,000 mg/dL, are the hallmark of the disease in FCS patients. However, given the low prevalence of this disease, to our knowledge, there are no well-conducted population-based studies that provide prevalence data for incidence and severity of pancreatitis and outcomes, including death. A survey was conducted among 21 highly experienced lipidologists responsible for the long-term care of 251 FCS patients throughout their careers. The lipidologists reported that recurrent abdominal pain not requiring hospitalisation occurred in 57% of patients, and led to hospitalisation that was not diagnosed as acute pancreatitis in 17% of patients. Hospitalisation for confirmed acute pancreatitis occurred in 67% of the FCS patients and half experienced recurrent acute pancreatitis, with 2 to 96 lifetime hospitalisations. Twelve (12) subjects (4.8%) died from acute pancreatitis (including children/teens aged 2, 11, and 18), with another patient dying during pregnancy. Long-term complications of recurrent acute pancreatitis, such as pancreatic insufficiency, diabetes, and

cardiorenal disease, accounted for 3 further deaths. Thus, total pancreatitis-related mortality was 6.0% (15/251) (Gaudet *et al.* 2016).

Mortality and morbidity

While data from Nawaz et al. noted in Figure 1 above represents mortality of those subjects who presented to the hospital with acute pancreatitis, it does not give insight into the risk per se for individual subjects (Nawaz *et al.* 2015). The survey data (Gaudet *et al.* 2016), conducted among lipidologists, suggests that for any given FCS subject, the risk of mortality from acute pancreatitis is ~ 6%. This is in contrast to those reported for 1981 subjects with multifactorial (non-FCS) chylomicronemia, for which 14% were hospitalised with acute pancreatitis and only 11 (0.55%) experienced pancreatitis-related deaths (Gaudet *et al.* 2016). Unlike FCS, the risk of acute pancreatitis from other (i.e., non-FCS) aetiologies of chylomicronemia, once identified, can usually be successfully mitigated by various medical interventions.

FCS is the third most common cause of pancreatitis, with an overall associated mortality of about 5% to 6% per episode (Fortson *et al.* 1995; Gaudet *et al.* 2016) but can reach as high as 10% to 30% if severe complications are present (Whitcomb 2006). While there is no correlation between the absolute maximal TG value and more severe pancreatitis episodes (Linares *et al.* 2008), a recent meta-analysis of observational studies found that HTG-induced acute pancreatitis is associated with a worse prognosis compared to pancreatitis of other causes (Wang *et al.* 2017). This includes a higher occurrence of renal failure, respiratory failure, shock, systemic inflammatory response syndrome, and higher Acute Physiology and Chronic Health Evaluation (APACHE-II) scores (Wang *et al.* 2017). Higher mortality rates are also reported for acute pancreatitis secondary to severe HTG (Deng *et al.* 2008; Wang *et al.* 2017), suggesting that HTG may worsen pancreatitis episodes. sHTG also carries an increased potential for developing atherosclerotic cardiovascular disease (ASCVD) (Hernandez *et al.* 2021; Hussain *et al.* 2022; Virani *et al.* 2021). 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).

Important Co-morbidities Found in the Target Population

Important co-morbidities in the target population include pancreatitis and diabetes. In the Phase 3 study of patients with FCS (ISIS 304801-CS6), 76% of patients had a history of pancreatitis, and 15% had a history of diabetes (Blom *et al.* 2018).

Studies also suggest that patients with FCS are susceptible to platelet count fluctuations over time and may also experience thrombocytopenia as part of the natural history of the disease (Larouche *et al.* 2023)

Recently presented longitudinal natural history data in 87 patients from 3 Canadian clinics (the SMASH registry) has shown that FCS patients may experience asymptomatic post-prandial fluctuations in platelet count over time, ranging from mild to severe thrombocytopenia to thrombocytosis (Gaudet *et al.* 2017; Witztum & Gaudet 2017). The majority (55%) of FCS patients exhibited thrombocytopenia on one or more occasions when followed over prolonged periods of time, including up to 17% exhibiting values $< 100 \times 10^9$/L and some as low as $< 50 \times 10^9$/L. In addition, 12% of FCS patients exhibited thrombocytosis ($> 450 \times 10^9$/L) (Table 3). In summary, there may be inherent variability in platelet counts in FCS patients (Gaudet *et al.* 2017; Witztum & Gaudet 2017).

In addition, FCS is associated with comorbidities similar to those arising as part of the disease process. These include frequent and intense abdominal pain, decreased cognition, anxiety, depression, and impaired social interactions (Brown *et al.* 2016), diffuse and ill-defined arthralgias, peripheral neuropathies, hepatosplenomegaly, diffuse erythema of the skin, and eruptive xanthomas. In addition, neuropsychiatric changes have been reported, including memory loss, the inability to think clearly ("fuzzy thinking"), difficulty in problem-solving (Chait *et al.* 1981), profound negative impact on the ability to work and interpersonal relationships with family and friends (Gardner *et al.* 2010).

There have also been reported cases of diminished quality of life, inability to work, as well as significant anxiety, fear and worry among patients with FCS. Patients also experience considerable time loss from work and a negative impact of the disease on their career choice due to complications of the disease (Davidson *et al.* 2017; 2018).

Patients also have a psychological burden from the awareness that they can pass on the disease to their children and a possible fear of the disease worsening during pregnancy for women, thus affecting their decisions about parenthood (Davidson *et al.* 2017; 2018). Pregnancy is a major challenge for any woman with FCS, as most often, they cannot tolerate birth control pills or estrogens, and death due to severe pancreatitis during pregnancy is well described (Gaudet *et al.* 2016; Montgomery & Miller 1970).

Table 3: Natural History of Thrombocytopenia or Thrombocytosis in Familial Chylomicronemia Syndrome (The SMASH Registry)[1,2]

Thrombocytopenia (Platelet count)	**N= 87 n (%)**	**Thrombocytosis (Platelet count)**	**N=87 n (%)**
Mild (100-149 × 10^9/L)	31 (35.6)	Mild (450-599 × 10^9/L)	6 (6.9)
Moderate (50-99 × 10^9/L)	15 (17.2)	Moderate (600–899 × 10^9/L)	4 (4.6)
Severe (< 50 × 10^9/L)	2 (2.4)	Severe (900-1000 × 10^9/L)	1 (1.1)
Total	48 (55.2)	Total	11 (12.6)

[1] (Witztum & Gaudet 2017);
[2] (Gaudet *et al.* 2017)

Part II: Module SII – Non-clinical part of the safety specification

A summary of key safety findings from non-clinical studies and relevance to human usage is presented below.

Toxicity

Olezarsen has the same nucleotide sequence, active moiety, and RNase H1 mechanism of action as volanesorsen, for which a full battery of toxicology testing has been completed. Olezarsen is a conjugated version of volanesorsen that is targeted specifically to the hepatocytes (Prakash *et al.* 2014) resulting in increased potency and tolerability with much larger safety margins. The exposure levels with olezarsen in non-clinical studies were similar or slightly less at mg/kg-equivalent doses compared with volanesorsen, but while volanesorsen was present primarily in nonparenchymal cells (e.g., Kupffer cells), olezarsen was present primarily in hepatocytes. There were no unexpected toxicities associated with hepatocyte-directed uptake, and no new toxicities were or could be attributable to the GalNAc conjugate.

The nonclinical toxicology program for olezarsen included repeat-dose studies in CD-1 mice and cynomolgus monkey of up to 26- and 39-week duration, respectively, with once-weekly subcutaneous administration. Reversibility of findings after a recovery period was evaluated in both the sub-chronic and chronic studies. Plasma and/or tissue pharmacokinetics were assessed as part of the toxicity evaluation. Additionally, a battery of *in vitro* and *in vivo* genotoxicity studies, a fertility and early embryonic development (FEED) study, and an impurity qualification study with olezarsen were conducted. Safety pharmacology studies of olezarsen included *in vitro* human Ether-à-go-go-related gene (hERG) assay and a study in monkeys to evaluate the potential effects on cardiovascular, respiratory, and central nervous system (CNS) function. The European Medicines Agency Committee for Medicinal Products for Human Use and the United States Food and Drug Administration (FDA) agreed to waive the requirement for an embryo-fetal development (EFD) studies in mouse and rabbit and pre-/postnatal toxicity study as well as mouse and rat carcinogenicity studies for olezarsen. These regulatory bodies determined that reproductive and development and carcinogenicity studies with olezarsen are not necessary as the results of the reproductive and development toxicity and carcinogenicity studies with volanesorsen are sufficient to conduct the risk assessment to support olezarsen.

Key Issues Identified from Acute or Repeat-dose Toxicity Studies

The spectra of olezarsen-related findings observed in mice and monkeys were, in general, non-specific class effects that are typical for a 2′-MOE ASO (Henry *et al.* 2008). The intended pharmacologic effect of dose dependent reduction in hepatic apoC-III mRNA levels (up to ~90% reductions) was achieved in monkeys and mice, and subsequent decreases in apoC-III plasma protein levels (up to ~90% reduction) in monkeys. There were no toxicological findings considered related to the pharmacologic inhibition of apoC-III expression.

Potential nonclinical safety issues identified during the development of olezarsen were limited in number and scope. These included severely decreased platelet count in a single monkey at 12 mg/kg/wk that was considered due to increased platelet clearance and minimal complement activation. Mild hepatic toxicity was limited to mice treated with ≥ 6 mg/kg/wk (24 mg/kg/month). These issues of decreased platelet and mild hepatic toxicity were considered to have minimal human relevance at clinically administered doses. The safety margins between

the no observed adverse effect level (NOAEL) at 6 mg/kg/wk in monkeys and the clinically relevant exposure (80 mg/month) are approximately ≥ 89.5-fold based on the cumulative plasma area under the curve (AUC) exposure.

Key safety findings from toxicity studies and their relevance to human usage are provided in Table 4.

Table 4: Key Safety Findings from Toxicity Studies and Relevance to Human Usage

Key Safety Findings (from Nonclinical Studies)	**Relevance to Human Usage**
Reductions in Platelet Counts The most noteworthy finding in the 13-week monkey study was a severely decreased platelet (PLT) count in one male in the 12 mg/kg/wk group. None of the other animals in any dose group up to 30 mg/kg/wk in the 13-week and up to 12 mg/kg/wk in the 39-week studies, respectively, demonstrated significant PLT reductions.	The low PLT count in this monkey is not attributed to either bone marrow toxicity or thrombosis, but most likely due to increased PLT clearance, most likely in the spleen. Importantly, the plasma AUC at 6 mg/kg/wk (24 mg/kg/month) in monkeys was approximately ≥ 89.5-fold higher than that for the clinical dose at 80 mg/month olezarsen. Therefore, this effect has minimal human relevance at the clinically administered doses.
Effects on Coagulation and Complement In the 13- and 39-week monkey study, there was acute and transient elevation of Bb levels which was accompanied by minimal to slight decreases in total C3 levels. The changes in C3 levels were dose-independent at pre-dose and 24 hours post-dose after 13 or 39 weeks of treatment when compared to baseline values. The concentration of plasma complement split product Bb was elevated by olezarsen treatment in an acute, transient, and dose-dependent pattern; an effect that has also been described for several 2′-MOE ASOs in the monkey; (Farman & Kornbrust 2003; Henry *et al.* 1997). However, complement C3 levels were dose-independent at pre-dose and 24 hours post-dose after 13 or 39 weeks of treatment when compared to baseline values.	Peak plasma ASO concentrations at the proposed clinical doses (up to 80 mg/month) will not reach plasma concentrations high enough for complement activation and aPTT, and the activation of alternative complement pathway is regarded as a monkey-specific effect of 2′-MOE ASO. Therefore, this effect is considered to have little to no relevance to humans (Shen *et al.* 2014).

Table 4: Key Safety Findings from Toxicity Studies and Relevance to Human Usage (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Effects on Coagulation and Complement (Continued) There were also slight transient prolongations in activated partial thromboplastin time (aPTT) (up to ~1.5-fold over baseline) at the 30 mg/kg/wk dose level which peaked at 4 to 8 hr post-dose on Day 1 and returned to baseline by 24 hours post-dose. This correlated with mean plasma olezarsen maximum serum concentrations (C_{max}) of approximately 86.5 to 118 µg/mL which were at least ~87-fold above the human exposure (C_{max} of approximately up to 1 µg/mL). Monkeys are more susceptible to complement activation relative to other species, including humans due to non-specific ASO-induced complement activation (Henry *et al.* 2002; 2014; Shen *et al.* 2014). Moreover, activation of the alternative complement pathway and aPTT in monkeys are driven by the plasma oligonucleotide C_{max} (Henry *et al.* 1997). The NOAEL for complement activation was considered 6 mg/kg/wk (C_{max} of approximately 16 µg/mL) which is approximately 16 times greater than the plasma C_{max} observed after SC injection of 50 or 80 mg olezarsen in patients (C_{max} of approximately up to 1 µg/mL). Peak plasma ASO concentrations at the proposed clinical doses (up to 80 mg/month) will not reach plasma concentrations high enough for complement activation, and the activation of alternative complement pathway is regarded as a monkey-specific effect of 2′-MOE ASO. (Shen *et al.* 2014).	
Immunogenicity Antibodies were detected in all dose groups at Days 91, 182, or 273 assessment and the incidence rate of positive immunogenicity (IM) per time point was 25.0% to 87.5% over a dose range of 2 to 30 mg/kg/wk. The impact on various PK, pharmacology, and toxicology parameters was assessed by stratifying animals based on the IM status and comparing parameters between those that were positive vs. negative.	Although plasma exposures were higher in IM positive animals compared to IM negative animals, there were no consistent differences in tissue concentrations. Thus, the IM had little to no effects on the pharmacology and toxicity findings in this study. There was no apparent correlation between pharmacology or toxicology endpoints and immunogenicity.

Table 4: Key Safety Findings from Toxicity Studies and Relevance to Human Usage (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Measurement of Anti-drug Antibody (Continued) The C_{max} and $AUC_{0\text{-}48h}$ following 39 weeks of treatment were 2- to 4-fold higher in IM positive animals compared to IM negative animals. The presence of anti-drug antibodies against olezarsen increased plasma trough concentrations. However, there were little to no notable differences in tissue levels of unconjugated olezarsen between IM negative and IM positive animals. In addition, complement C3, PLT counts, hepatic apoC-III mRNA levels and microscopic findings were similar in both IM positive and negative monkeys after up to 39 weeks of treatment. There was no apparent correlation between toxicology or pharmacology endpoints and immunogenicity.	
Additional Treatment-related Effects Additional treatment-related effects were observed, including the presence of basophilic granules in the kidney, liver, and in resident macrophages in various tissues, particularly lymph nodes. The accumulation of basophilic granules in the liver of both mice and monkeys was associated with slight increases in liver weights at the high doses in the studies.	The presence of basophilic granules is attributed to the uptake and accumulation of ASO in tissues. Nucleic acids, such as 2′-MOE ASOs (e.g., olezarsen) stain with haematoxylin and therefore their uptake into cells can be visualised microscopically as basophilic granules (Butler *et al.* 1997). Thus, basophilic granules in tissue are indicative only of the presence of oligonucleotide in organs where compound exposure is the greatest (liver and kidney) and are not considered adverse in nature (Henry *et al.* 2008).

Reproductive/Developmental Toxicity

A fertility and early embryonic development (FEED) assessment for olezarsen was performed in mice based on slightly decreased organ weight in prostate/seminal vesicle and decreased sperm count finding on the previous combined FEED/EFD mouse study with volanesorsen. The completed FEED study with olezarsen showed the absence of any FEED toxicity, similar to results from previous studies with volanesorsen and other 2′-MOE ASOs with and without GalNAc conjugations (Cavagnaro *et al.* 2014; Henry *et al.* 2004).

Antisense oligonucleotides, such as olezarsen, are not easily transported across the placenta because of their size, molecular charge, water solubility, and high plasma protein binding.

Based on these findings, no risks on reproductive or developmental effects are anticipated with olezarsen; however, as pregnant participants were excluded from olezarsen clinical studies, this is regarded as an area of missing information until such time further data can be obtained in the clinical setting.

Genotoxicity

Olezarsen was not genotoxic in the bacterial reverse mutation assay, the chromosome aberration assay in Chinese hamster lung cells, and the mouse bone marrow micronucleus assay.

Carcinogenicity

No carcinogenicity studies were conducted with olezarsen based on the results of the carcinogenicity studies with volanesorsen, which were sufficient to conduct the risk assessment to support similar product labeling for olezarsen.

Based on the aggregate results of carcinogenicity studies conducted with volanesorsen in mice and rats along with the overall similarities in sequence, chemistry, toxicokinetic, and chronic toxicity profiles of volanesorsen and olezarsen, olezarsen is interpreted to pose little or no carcinogenic risk for patients.

Toxicology studies for olezarsen provided data to define target organ systems and dose-effect relationships and formed the basis for an adequate level of understanding of the potential toxicities of chronic exposure in a therapeutic setting. Effects of olezarsen were reversible and exhibited no evidence of delayed or recurring toxicity. In addition, there was no evidence of increased severity of target organ toxicity once steady-state tissue concentrations were achieved. The exposure levels in subchronic/chronic studies (weekly dose) with olezarsen were similar or slightly less at mg/kg-equivalent doses compared with volanesorsen, and no new toxicities were observed with olezarsen.

Safety Pharmacology

Olezarsen had no effects on safety pharmacology parameters including CNS, heart and respiratory, and no blocking of hERG current. Thus, there were no safety concerns identified for these organ systems in nonclinical studies.

Part II: Module SIII – Clinical trial exposure

Exposure to olezarsen is based on all patients who have received at least one dose of olezarsen in the 3 FCS population studies (pooled): ISIS 678354-CS3, ISIS 678354-CS7 and ISIS 678354-CS13. Of note, study ISIS 678354-CS13 is an ongoing open-label extension study of patients rolling over from ISIS 678354-CS3. As of 01 Dec 2023, a total of 89 patients in these FCS population studies have been exposed to olezarsen.

Tables presented in this section represent pooled exposure data from the following FCS population studies:

- ISIS 678354-CS3 (Pivotal study): A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ISIS 678354 Administered Subcutaneously to Patients with FCS
- ISIS 678354-CS7: An Open-Label Safety Study of AKCEA-APOCIII-L_{RX}, Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS) Previously Treated with Volanesorsen (ISIS 304801)
- ISIS 678354-CS13: An Open-Label Extension Study of AKCEA-APOCIII-L_{RX} Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Table 5: Duration of Exposure For All FCS Population Studies (Olezarsen Treated Set)

Duration of Exposure	Patients n (%)	Person Time (Years)
Olezarsen 50 mg/80 mg (N = 21)		
< 6 months	2 (9.5)	0.48
>= 6 months to < 12 months	0	0
>= 12 months to < 24 months	10 (47.6)	16.70
>= 24 to < 36 months	8 (38.1)	18.61
>= 36 to < 42 months	1 (4.8)	2.96
Total	21 (100.0)	38.75
Olezarsen 80 mg (N = 68)		
< 6 months	10 (14.7)	2.44
>= 6 months to < 12 months	12 (17.6)	8.60
>= 12 months to < 24 months	34 (50.0)	50.35
>= 24 to < 36 months (1080 days)	12 (17.6)	26.77
>= 36 to < 42 months	0	0
Total	68 (100.0)	88.16
Total Olezarsen (N = 89)		
< 6 months	12 (13.5)	2.92
>= 6 months to < 12 months	12 (13.5)	8.60
>= 12 months to < 24 months	44 (49.4)	67.05
>= 24 to < 36 months	20 (22.5)	45.38
>= 36 to < 42 months	1 (1.1)	2.96
Total	89 (100.00)	126.90

N = number of safety patients in treatment group; n = number of patients in the specified category; %=n/N*100.
For patients no longer on study drug at the time of data cutoff for the ISS, duration of exposure (years) = (last dose date – first dose date + 28)/365.25. For patients on study drug at the time of the data cutoff for the ISS, duration of exposure (years) = (minimum of (last dose date + 28, data cutoff date + 1) - first dose date)/365.25.
Note 1: Person Time (Years) was the sum of duration of exposure (years) for all patients in the category.
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 were analyzed together.
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 initially randomized to ISIS 678354 80 mg and then had their dose reduced to 50 mg are included in the olezarsen 80 mg group.

Table 6: Exposure by Age Group and Gender All FCS Population Studies (Olezarsen Treated Set)

	Patients n (%)		Person Time (Years)	
Treatment Age Group	Male	Female	Male	Female
Olezarsen 50 mg/80 mg (N = 21)				
Children (< 18 years)	0	0	0	0
Adults (18–64 years)	6 (100.0)	14 (19.3)	12.49	26.10
Elderly people	0	1 (6.7)	0	0.16
65-74 years	0	1 (6.7)	0	0.16
75-84 years	0	0	0	0
85+ years	0	0	0	0
Total	6 (100.0)	15 (100.0)	12.49	26.26
Olezarsen 80 mg (N = 68)				
Children (< 18 years)	0	0	0	0
Adults (18–64 years)	27 (84.4)	33 (91.7)	37.56	42.22
Elderly people	5 (15.6)	3 (8.3)	6.46	1.93
65-74 years	5 (15.6)	2 (5.6)	6.46	1.54
75-84 years	0	1 (2.8)	0	0.39
85+ years	0	0	0	0
Total	32 (100.0)	36 (100.0)	44.01	44.15
Total Olezarsen (N = 89)				
Children (< 18 years)	0	0	0	0
Adults (18–64 years)	33 (86.8)	47 (92.2)	50.05	68.32
Elderly people	5 (13.2)	4 (7.8)	6.46	2.08
65-74 years	5 (13.2)	3 (5.9)	6.46	1.70
75-84 years	0	1 (2.0)	0	0.39
85+ years	0	0	0	0
Total	38 (100.0)	51 (100.0)	56.50	70.40

N = number of safety patients in treatment group; n = number of patients in the specified category; %=n/N*100.
For patients no longer on study drug at the time of data cutoff for the ISS, duration of exposure (years) = minimum of (last dose date – first dose date + 28)/365.25. For patients on study drug at the time of the data cutoff for the ISS, duration of exposure (years) = minimum of (last dose date + 28, data cutoff date + 1) - first dose date)/365.25.
Note 1: Person Time (Years) was the sum of duration of exposure (years) for all patients in the category.
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 were analyzed together.
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 initially randomized to ISIS 678354 80 mg and then had their dose reduced to 50 mg are included in the olezarsen 80 mg group.

Table 7: Exposure by Race All FCS Population Studies (Olezarsen Treated Set)

Treatment Race	Patients n (%)	Person Time (Years)
Olezarsen 50 mg/80 mg (N =21)		
Asian	3 (14.3)	5.79
Native Hawaiian or Other Pacific Islander	1 (4.8)	1.40
White	17 (81.0)	31.56
Other	0	0
Total	21 (100.0)	38.75
Olezarsen 80 mg (N = 68)		
Asian	5 (7.4)	7.60
Native Hawaiian or Other Pacific Islander	0	0
White	59 (86.8)	74.33
Other	4 (5.9)	6.23
Total	68 (100.0)	88.16
Total Olezarsen (N = 89)		
Asian	8 (9.0)	13.39
Native Hawaiian or Other Pacific Islander	1 (1.1)	1.40
White	76 (85.4)	105.89
Other	4 (4.5)	6.23
Total	89 (100.0)	126.90

N = number of safety patients in treatment group; n = number of patients in the specified category; %=n/N*100.
For patients no longer on study drug at the time of data cutoff for the ISS, duration of exposure (years) = (last dose date – first dose date + 28)/365.25. For patients on study drug at the time of the data cutoff for the ISS, duration of exposure (years) = (minimum of (last dose date + 28, data cutoff date + 1) - first dose date)/365.25.
Note 1: Person Time (Years) was the sum of duration of exposure (years) for all patients in the category.
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 were analyzed together.
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 ISIS 678354 80 mg and then had their dose reduced to 50 mg.

Table 8: Exposure by Ethnic Origin All FCS Population Studies (Olezarsen Treated Set)

Treatment Ethnicity	Patients n (%)	Person Time (Years)
Olezarsen 50 mg/80 mg (N = 21)		
Hispanic or Latino	3 (14.3)	6.81
Not Hispanic or Latino	18 (85.7)	31.93
Total	21 (100.0)	38.75
Olezarsen 80 mg (N = 68)		
Hispanic or Latino	3 (4.4)	4.34
Not Hispanic or Latino	65 (95.6)	83.82
Total	68 (100.0)	88.16
Total Olezarsen (N = 89)		
Hispanic or Latino	6 (6.7)	11.15
Not Hispanic or Latino	83 (93.3)	115.75
Total	89 (100.0)	126.90

N = number of safety patients in treatment group; n = number of patients in the specified category; %=n/N*100.
For patients no longer on study drug at the time of data cutoff for the ISS, duration of exposure (years) = (last dose date – first dose date + 28)/365.25. For patients on study drug at the time of the data cutoff for the ISS, duration of exposure (years) = (minimum of (last dose date + 28, data cutoff date + 1) - first dose date)/365.25.
Note 1: Person Time (Years) was the sum of duration of exposure (years) for all patients in the category.
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 were analyzed together.
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 initially randomized to ISIS 678354 80 mg and then had their dose reduced to 50 mg are included in the olezarsen 80 mg group.

Part II: Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

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.

Reason for Exclusion:

Patients with clinically significant abnormalities in medical history were excluded to avoid factors that may confound a complete understanding of the safety and efficacy data of olezarsen and to ensure interpretability of the data.

Is it considered missing information? No

Rationale:

There is no scientific rationale to suspect that the safety profile of olezarsen in this patient population may differ from that characterised so far in the general target population.

Active pancreatitis within 4 weeks prior to screening

Reason for Exclusion:

Patients with active pancreatitis within 4 weeks prior to screening were excluded, as this would interfere with interpretation and assessment of efficacy.

Is it considered missing information? No

Rationale:

There is no scientific rationale to suspect that the safety profile of olezarsen in this patient population may differ to that characterised so far in the general target population.

Platelet count < 100K/mm^3 at screening or qualification; History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at screening

Reason for Exclusion:

Volanesorsen is associated with reductions in platelet counts, which may result in thrombocytopenia, as described in the Waylivra summary of product characteristics (SmPC).

Patients with history of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters were excluded to avoid factors that may confound a complete understanding of the safety data of olezarsen and ensure interpretability of data.

Is it considered missing information? No

Rationale:

Safety data do not suggest that olezarsen has a clinically meaningful effect on platelet counts. No patients met the predefined stopping rules regarding platelet counts, or discontinued treatment due to thrombocytopenia, no patients experienced a concurrent serious or severe bleeding event due to thrombocytopenia, and no patients treated with olezarsen had severe platelet count reductions.

Blood donation of 50 to 499 mL, within 30 days of screening or of > 499 mL within 60 days of screening

Reason for Exclusion: To limit the amount of blood taken during a 30- or 60-day period, as there are per protocol required blood draws, as well as screening and qualification visit blood draws.

Is it considered missing information? No

Rationale:

There is no scientific rationale to suspect that the safety profile in this patient population may differ to that characterized so far in the general target population.

Hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3.0 × upper limit of normal [ULN]; Total bilirubin > ULN unless due to Gilbert's syndrome)

Reason for Exclusion:

Patients with active hepatic injury with ALT/AST > 3 × ULN were excluded to avoid treatment of patients with active liver disease, as this could interfere with interpretation and assessment of efficacy and safety endpoints in a population who may have an underlying metabolic liver disease.

Is it considered missing information? No

Rationale:

Overall evaluation of adverse event (AE) and laboratory data does not suggest a clinically meaningful effect of olezarsen on liver function. No safety concerns have been identified related to hepatic impairment. Based on this data, there is no scientific rationale to suspect that the safety profile in this patient population may differ to that characterised thus far in the general target population.

Renal impairment (Estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m^2; Urine protein/creatinine ration [UPCR] > 500 mg/g, or urine albumin/creatinine [UACR] ratio > 300 mg/g)

Reason for Exclusion:

This population was excluded to avoid factors that may confound a complete understanding of the safety data of olezarsen and to ensure interpretability of the data, and should only be used in these patients if the anticipated clinical benefit outweighs the risk.

Is it considered missing information? No

Rationale:

No safety concerns have been identified relating to renal function in clinical studies and no dose adjustment is necessary in patients with mild to moderate renal impairment as defined by eGFR ≥ 45 to < 90 mL/min/1.73 m^2. Olezarsen has not been studied in patients with severe renal impairment or end-stage renal disease.

There is no scientific rationale to suspect that the safety profile in this patient population may differ to that characterised thus far in the general target population.

Overall evaluation of AE and laboratory data does not suggest a clinically meaningful effect of olezarsen on renal function. No safety concerns have been identified related to renal impairment.

Uncontrolled arterial hypertension (Blood Pressure > 160/100 mm Hg)

Reason for Exclusion:

Patients with uncontrolled hypertension were excluded to avoid factors that may confound a complete understanding of the safety and efficacy data.

Is it considered missing information? No

Rationale:

No clinically meaningful trends or safety concerns were observed in any treatment group across all olezarsen clinical studies related to blood pressure.

Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 or active COVID-19 infection with or without therapy that will not be resolved by Study Day 1

Reason for Exclusion:

Patients with an active infection requiring systemic antiviral or antimicrobial therapy were excluded to avoid factors that may confound a complete understanding of the safety data of olezarsen.

Is it considered missing information? No

Rationale:

There is no scientific rationale to suspect that the safety profile in this patient population may differ to that characterised thus far in the general target population.

Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B

Reason for Exclusion:

Patients with a known history of or a positive test for HIV, hepatitis C, or hepatitis B were excluded to avoid the potential confounding effect of the natural history of these conditions on a complete understanding of the safety data of olezarsen.

Is it considered missing information? No

Rationale:

The anticipated use in patients with FCS and a known history of or positive test for HIV, hepatitis C, or hepatitis B is expected to be very low as this population is rare. This population is therefore not relevant for consideration as missing information.

Malignancy within 5 years except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated.

Reason for Exclusion:

This population was excluded to omit factors that may impact the interpretability of the olezarsen data.

Is it considered missing information? No

Rationale:

There is no scientific rationale to suspect that the safety profile of olezarsen in this patient population may differ to that characterised thus far in the general target population.

Pregnant and /or Lactating Patients

Reason for Exclusion:

Patients who are pregnant and/or lactating were excluded from participating in clinical trials in order to avoid potential harm to the unborn foetus or breastfed infant.

Is it considered missing information? Yes (Use in pregnancy), No (Use in lactation)

Rationale:

It is not known whether olezarsen or its metabolites are excreted in human milk or have effects on a breastfed infant or milk production. It should be noted that due to the poor oral bioavailability of ASO and the low dose of olezarsen treatment (i.e., 80 mg every month), no potential clinical impact on a breastfed child from the carry-over of olezarsen in breast milk is anticipated. Furthermore, given the rarity of the disease in addition to the expected very low use of olezarsen in breastfeeding women, evaluation of the safety profile in this population is not feasible. For these reasons, only use in pregnancy is considered missing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, and adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 9: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: Patient with hepatic impairment *(ALT or AST > 3×ULN and/or total bilirubin > ULN unless due to Gilbert's syndrome)* Patients with renal impairment *(eGFR < 45 mL/min/1.73 m^2)* Patients with clinically significant abnormalities in medical history *(e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening)* Immunocompromised patients *(active infections with HIV, HCV, HBV, or requiring systemic antivirals, or malignancy within 5 years)*	Not included in the clinical development program
Patients with relevant different ethnic origin	In CS3, a total of 43 patients were in the olezarsen treatment set. The majority of patients had their ethnicity recorded as Not Hispanic or Latino, 39 (90.7%) vs. Hispanic or Latino 4 (9.3%). In the FCS patient population, a total of 89 patients were in the olezarsen treatment set. The majority of patients had their ethnicity recorded as Not Hispanic or Latino, 83 (93.3%) vs. Hispanic or Latino 6 (6.7%).

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Olezarsen does not cross the blood-brain barrier after subcutaneous administration and has no known effects on the central nervous system. There are no data to suggest that there is a potential for olezarsen to be misused for illegal purposes.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

SVII.1.1.1 Known risks that do not impact the risk-benefit profile:

- Injection site reactions

  Across clinical studies in the FCS population, injection site reactions (ISRs) were more commonly observed in olezarsen-treated patient groups than placebo. The most frequently reported ISRs (in more than 1 patient) included Injection site erythema, injection site discoloration, Injection site pain, and Injection site swelling. All ISRs were local and did not result in systemic sequelae, were mild or moderate in severity, not observed after every injection, were self-limiting and did not require treatment, and none resulted in permanent discontinuation or dose reduction of olezarsen in patients with FCS. These ISRs are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

- Chills

  Across clinical studies in the FCS population, treatment-emergent adverse events (TEAEs) of Chills were non-serious (mostly mild in severity), only observed in olezarsen-treated patients, resolved spontaneously, were nonprogressive, and did not require treatment. No action was taken with the study drug due to Chills except for 1 patient in study CS3 who was permanently discontinued from the study due to Chills and Myalgia. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

- Myalgia

  Across clinical studies in the FCS population, TEAEs of Myalgia were non-serious (mostly mild in severity), only observed in olezarsen-treated patients, resolved spontaneously, were nonprogressive, and did not require treatment. No action was taken with the study drug due to Myalgia except for 1 patient in study CS3 who was permanently discontinued from the study due to Chills and Myalgia (same patient described under Chills). These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

- Arthralgia

  Across clinical studies in the FCS population, treatment-emergent adverse events (TEAEs) of arthralgia were observed. All events were non-serious, mostly mild in severity, and no patient had positive rechallenge with continued treatment. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

- Hypersensitivity

  Across clinical studies in the FCS population, Hypersensitivity has been observed with olezarsen. Hypersensitivity related events were generally mild or moderate in severity and did not require dose reduction. Severe hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias) have been observed in 2 patients in clinical studies. In both patients, the event was acute, required treatment, and resulted in treatment discontinuation. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

- Headache

  Across clinical studies in the FCS population, treatment-emergent adverse event (TEAE) of headache has been observed more frequently among the olezarsen group than the placebo group. TEAEs of headache were mostly mild in severity and no patients discontinued treatment as a result of headache. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

- Vomiting

  Across clinical studies in the FCS population, treatment-emergent adverse event (TEAE) of vomiting was only observed in olezarsen-treated patients. The majority of vomiting related events were mild in severity, did not require treatment, and did not result in a positive rechallenge. Only 1 patient discontinued treatment. This patient was in the pivotal CS3 study with concurrent asymptomatic COVID-19, had additional events that collectively resulted in treatment discontinuation. All patients who experienced vomiting in the pivotal CS3 study and rolled over to the open-label extension study (OLE), 678354-CS13, did not experience a recurrence of vomiting. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks:

There are no important identified risks for olezarsen.

Important Potential Risks:

Hepatotoxicity, Renal Toxicity, Thrombocytopenia

Risk Benefit Impact:

Reasons for inclusion:

There are limited safety data available on the use of olezarsen in patients with FCS at the time of marketing authorisation. Adverse effects observed after the administration of some antisense oligonucleotides, including thrombocytopenia, hepatotoxicity and renal toxicity, were not observed during clinical development of olezarsen but cannot be completely excluded and are therefore added as important potential risks to the RMP.

Missing Information:

Use in pregnancy

Risk-benefit impact: There are no data on the use of olezarsen in pregnant women. Based on animal data, olezarsen is predicted to have a low probability of increasing the risk of adverse developmental outcomes above background risk.

Long-term safety

Risk-benefit impact: Safety data to date from patients who have been exposed to olezarsen showed that olezarsen is well tolerated; however, its use has not been assessed in patients for long durations of time.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified risks for olezarsen.

There are 3 important potential risks for olezarsen: Hepatotoxicity, Renal Toxicity, and Thrombocytopenia.

Important Potential Risk – Hepatotoxicity	
Potential mechanisms	No serious risk of hepatotoxicity was identified during clinical development with olezarsen. The liver is the site of accumulation of antisense oligonucleotides (ASOs), hepatotoxicity has been observed with some antisense oligonucleotides and therefore cannot be completely excluded. The exact mechanism is currently unknown.
Evidence source(s) and strength of evidence	In chronic toxicology studies in non-human primates, olezarsen was not associated with hepatotoxicity. Olezarsen was not associated with hepatotoxicity during clinical trials in patients with FCS (Studies ISIS 678354-CS3, ISIS 678354-CS7, and ISIS 678354-CS13) (patient exposure n=89) in olezarsen vs. placebo (patient exposure n=23).
Characterisation of the risk	Events of hepatotoxicity were identified using the following search strategy: MedDRA SMQ Drug related hepatic disorders - comprehensive search. Results of clinical studies evaluating olezarsen have not shown any liver-related adverse effects that required additional monitoring. Review of safety data in all patients with FCS (Studies ISIS 678354-CS3, ISIS 678354-CS7, and ISIS 678354-CS13) showed a lower rate of hepatic related events, including abnormal liver function tests, in the total olezarsen group (7.9%) compared with the placebo group (13.0%). Hepatic-related events were generally mild to moderate in severity, were not considered clinically meaningful, and none led to study drug discontinuation. Safety data do not suggest that olezarsen has a clinically meaningful effect on liver function or is associated with a risk of drug-induced liver injury in patients with FCS.
Risk factors and risk groups	Alcohol consumption, underlying comorbidities such as type 2 diabetes, Metabolic Dysfunction-Associated Steatohepatitis (MASH), hepatitis, autoimmune diseases, exposure to hepatotoxins or hepatotoxic materials/drugs, malnutrition, and herbal supplements not approved by healthcare provider.
Preventability	Avoidance of known risks factors such as hepatotoxic medications and routine laboratory testing as per standard of care.
Impact on the risk- benefit balance of the product	No correlation has been identified between hepatotoxicity and safety or efficacy measures in olezarsen clinical studies.
Public health impact	Potential of public health impact is low.

Important Potential Risk – Renal toxicity	
Potential mechanisms	No serious risk of renal toxicity was identified during clinical development with olezarsen. The exact mechanism is currently unknown.
Evidence source(s) and strength of evidence	Olezarsen has not been associated with renal toxicity based on completed chronic renal toxicology studies in non-human primates. Olezarsen was not associated with renal toxicity during Clinical trials CS3 + CS13 + CS7 (patient exposure n=89) in olezarsen vs. placebo (patient exposure n=23).
Characterisation of the risk	Renal toxicity adverse effects were identified using the following methodology: MedDRA search criteria: SMQ Acute renal failure (broad and narrow). Across all FCS population trials, a greater proportion of patients in the placebo group (8.7%) experienced renal toxicity events, compared with the olezarsen 80 mg group (4.5%) and none in the olezarsen 50 mg/80 mg group. No patient experienced a serious renal toxicity event, or was permanently discontinued from study drug due to a renal toxicity event. The proportion of patients experiencing eGFR reduction of ≥ 25% and ≥ 30% from Baseline was higher in the placebo group (27.9% and 17.4%, respectively) than in the total olezarsen groups (19.9% and 10.6%, respectively). Similarly, the proportion of patients experiencing UACR ≥ 300 mg/g and UPCR ≥ 500 mg/g was similar or higher in the placebo group (7.0% and 16.3%, respectively) than in the total olezarsen group (7.9% and 11.0%, respectively). Safety data do not suggest that olezarsen treatment has a clinically meaningful impact on renal function.
Risk factors and risk groups	Underlying cardiac and renal comorbidities, dehydration, diabetes mellitus, infections, and nephrotoxic medications.
Preventability	Avoidance of known risks factors such as nephrotoxic medications and routine laboratory testing as per standard of care.
Impact on the risk- benefit balance of the product	No correlation has been identified between renal toxicity and safety or efficacy measures in olezarsen clinical studies.
Public health impact	Potential of public health impact is low.

Important Potential Risk – Thrombocytopenia	
Potential mechanisms	No serious risk of thrombocytopenia was identified during clinical development with olezarsen. Thrombocytopenia has been observed with some antisense oligonucleotides. An extensive investigation to evaluate the potential cause of thrombocytopenia/ platelet count changes has been conducted with unconjugated ASOs (olezarsen is a conjugated 2′-MOE ASO).
Evidence source(s) and strength of evidence	Olezarsen has not been associated with thrombocytopenia based on completed chronic toxicology studies in non-human primates. Olezarsen was not associated with thrombocytopenia in patients with FCS (Studies ISIS 678354-CS3, ISIS 678354-CS7, and ISIS 678354-CS13) (patient exposure n=89) in olezarsen vs. placebo (patient exposure n=23). No patients met the predefined stopping rule regarding platelet counts, or discontinued treatment due to a thrombocytopenia TEAE, and no patients with platelet count < LLN experienced a concurrent serious or severe bleeding event. Although a greater proportion of patients in the olezarsen treatment groups experienced platelet reductions of ≥ 30% from Baseline or platelet counts in the range of ≥ 75,000 to < 140,000/mm^3 compared with the placebo group, the proportion of patients who experienced platelet reductions of ≥ 50% or counts < 75,000/mm^3 was similar between both olezarsen treatment groups and the placebo group.
Characterisation of the risk	Events of thrombocytopenia were identified by the following search criteria: PT: Thrombocytopenia PT: Platelet count decreased Across all FCS population studies TEAEs of thrombocytopenia were observed in a greater proportion of patients in the olezarsen 50 mg/80 mg treatment group (9.5%) and olezarsen 80 mg treatment group (5.9%), compared with the placebo group (4.3%). There were no serious or severe TEAEs of thrombocytopenia. TEAEs in the olezarsen treatment groups, and platelet count changes were not associated with increased bleeding risk. No patient treated with olezarsen experienced a platelet count of < 50,000/mm^3, compared to placebo (4.3%). Variability in platelet counts over time is considered as part of the natural history of the disease in the FCS patient population (Gaudet *et al.* 2017).
Risk factors and risk groups	Patients with thrombocytopenia < 100 × 10^9/L.
Preventability	Routine laboratory testing as per standard of care.
Impact on the risk- benefit balance of the product	No correlation has been identified between thrombocytopenia and safety or efficacy measures in olezarsen clinical studies.
Public health impact	Potential of public health impact is low.

SVII.3.2 Presentation of the missing information

Missing information: Use in Pregnancy

Evidence source:

There are no available data on TRYNGOLZA use in pregnant women to inform drug-associated risk of adverse developmental outcomes.

Based on animal data, TRYNGOLZA is predicted to have a low probability of increasing the risk of adverse developmental outcomes above background risk.

Population in need of further characterisation:

Pregnant women with FCS who have been exposed to TRYNGOLZA.

Missing information: Long-term Safety

Evidence source:

Treatment with olezarsen is expected to be lifelong; however, its use has not been assessed in patients for long periods of time.

As of date 01 Dec 2023, 12 (13.5%) of patients with FCS received olezarsen for < 6 months; 12 (13.5%) received olezarsen for ≥ 6 to < 12 months; most patients in clinical studies received olezarsen for ≥ 12 to < 24 months (44 [49.4%] patients); 20 (22.5%) patients received olezarsen for ≥ 24 to < 36 months; and 1 (1.1%) patient received olezarsen for ≥ 36 months to < 42 months.

As long-term use of TRYNGOLZA is needed to provide therapeutic benefit in patients with FCS, the limited long-term safety data in olezarsen-treated patients with FCS warrants inclusion of long-term safety as missing information.

Population in need of further characterisation:

FCS patients with long-term treatment with TRYNGOLZA

Part II: Module SVIII – Summary of the safety concerns

Table 10: 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 safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific targeted follow-up questionnaires for Hepatotoxicity, Renal Toxicity, and Thrombocytopenia.

A specific targeted follow-up questionnaire will be used to obtain further information regarding reported suspected adverse reactions of Hepatotoxicity, Renal Toxicity, and Thrombocytopenia events. The questionnaires have been designed to collect additional information pertaining to the clinical course of the event, the signs and symptoms observed, olezarsen treatment received, relevant medical history, concomitant medications, risk factors, treatment received for the event, and relevant laboratory results.

Other forms of routine pharmacovigilance activities:

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2 Additional pharmacovigilance activities

Not Applicable.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine risk minimisation measures

Table 11: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Potential Risk	
Hepatotoxicity	Routine risk communication: • SmPC Section 4.4 • PL Section 2.0 Routine risk minimisation measures: • None Legal status: • Medicinal product subject to medical prescription Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up Questionnaire Additional risk minimisation measures: • None Additional pharmacovigilance activities: • None
Renal Toxicity	Routine risk communication: • SmPC Section 4.4 • PL Section 2.0 Routine risk minimisation measures: • None Legal status: • Medicinal product subject to medical prescription Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up Questionnaire Additional risk minimisation measures: • None Additional pharmacovigilance activities: • None
Thrombocytopenia	Routine risk communication: • SmPC Section 4.4 • PL Section 2.0 Routine risk minimisation measures: • None Legal status: • Medicinal product subject to medical prescription Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up Questionnaire Additional risk minimisation measures: • None Additional pharmacovigilance activities: • None

Table 11: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety concern	Routine risk minimisation activities
Missing Information	
Use in pregnancy	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Instructions to seek medical advice before using olezarsen during pregnancy are included in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: prescription only medication
Long-term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None

V.2 Additional risk minimisation measures

There are no Additional Risk Minimisation Measures, routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 12: 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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for TRYNGOLZA (olezarsen)

This is a summary of the risk management plan (RMP) for TRYNGOLZA. The RMP details important risks of TRYNGOLZA, how these risks can be minimised, and how more information will be obtained about TRYNGOLZA's risks and uncertainties (missing information).

TRYNGOLZA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TRYNGOLZA should be used.

This summary of the RMP for TRYNGOLZA should be read in the context of all this information including the assessment report of the evaluations and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TRYNGOLZA's RMP.

I: The medicine and what it is used for

TRYNGOLZA is authorised as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS) to reduce triglycerides and the rate of acute pancreatitis events (see SmPC for the full indication). It contains olezarsen as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of TRYNGOLZA's benefits can be found in TRYNGOLZA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II: Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TRYNGOLZA, together with measures to minimise such risks and the proposed studies for learning more about TRYNGOLZA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size – the amount of medicine in a pack – is chosen so to ensure that the medicine is used correctly
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) – can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of TRYNGOLZA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TRYNGOLZA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TRYNGOLZA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Hepatotoxicity Renal Toxicity Thrombocytopenia
Missing information	Use in pregnancy
	Long-term safety

II.B Summary of important risks

Important Identified Risk – None	
Important Potential Risk – Hepatotoxicity	
Evidence for linking the risk to the medicine	In chronic toxicology studies in non-human primates, olezarsen was not associated with hepatotoxicity. Olezarsen was not associated with hepatotoxicity during clinical trials in patients with FCS (Studies ISIS 678354-CS3, ISIS 678354-CS7, and ISIS 678354-CS13) (patient exposure n=89) in olezarsen vs. placebo (patient exposure n=23).
Risk factors and risk groups	Alcohol consumption, underlying comorbidities such as type 2 diabetes, Metabolic Dysfunction-Associated Steatohepatitis (MASH), hepatitis, autoimmune diseases, exposure to hepatotoxins or hepatotoxic materials/drugs, malnutrition, and herbal supplements not approved by healthcare provider.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None
Important Potential Risk – Renal toxicity	
Evidence for linking the risk to the medicine	Olezarsen has not been associated with renal toxicity based on completed chronic renal toxicology studies in non-human primates. Olezarsen was not associated with renal toxicity during Clinical trials CS3 + CS13 + CS7 (patient exposure n=89) in olezarsen vs. placebo (patient exposure n=23).
Risk factors and risk groups	Underlying cardiac and renal comorbidities, dehydration, diabetes mellitus, infections, and nephrotoxic medications.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None

Important Potential Risk – Thrombocytopenia	
Evidence for linking the risk to the medicine	Olezarsen has not been associated with thrombocytopenia based on completed chronic toxicology studies in non-human primates. Olezarsen was not associated with thrombocytopenia in patients with FCS (Studies ISIS 678354-CS3, ISIS 678354-CS7, and ISIS 678354-CS13) (patient exposure n=89) in olezarsen vs. placebo (patient exposure n=23). No patients met the predefined stopping rule regarding platelet counts, or discontinued treatment due to a thrombocytopenia TEAE, and no patients with platelet count < LLN experienced a concurrent serious or severe bleeding event. Although a greater proportion of patients in the olezarsen treatment groups experienced platelet reductions of ≥ 30% from Baseline or platelet counts in the range of ≥ 75,000 to < 140,000/mm^3 compared with the placebo group, the proportion of patients who experienced platelet reductions of ≥ 50% or counts < 75,000/mm^3 was similar between both olezarsen treatment groups and the placebo group.
Risk factors and risk groups	Patients with thrombocytopenia < 100 × 109/L.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None
Missing information – Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 • Legal status: prescription only medication Additional risk minimisation measures: • None
Missing information – Long term safety	
Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimisation measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for TRYNGOLZA.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for TRYNGOLZA.

PART VII: ANNEXES

Table of Contents

Version	Change
0.1	Initial RMP version.
0.2	SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP: Updated to remove Hypersensitivity as an important potential risk. Part VII: Annexes Annex 4 – Specific adverse drug reaction follow-up forms Updated to remove Hypersensitivity follow-up form.
0.3	SVII.1.1.1 Known risks that do not impact the risk-benefit profile: section updated to include: Headache, Vomiting, and Hypersensitivity. Long term safety: Updated throughout the document to remove the wording: "including renal toxicity, hepatotoxicity, and thrombocytopenia" Indication updated to: TRYNGOLZA (olezarsen) is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).
0.4	SVII.3 Details of important identified risks, important potential risks, and missing information updated to include Hepatotoxicity, Renal Toxicity, and Thrombocytopenia as important potential risks. Part II: Module SVIII - Summary of the safety concerns updated to include Hepatotoxicity, Renal Toxicity, and Thrombocytopenia as important potential risks. III.1 Routine Pharmacovigilance Activities Table Part V.1: Description of routine risk minimisation measures by safety concern updated to include: Specific targeted follow-up questionnaires for Hepatotoxicity, Renal Toxicity, and Thrombocytopenia. Table Part V.1: Description of routine risk minimisation measures by safety concern: table updated to include information on Routine risk communication and minimisation measure, legal status, and Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, for the three important potential risks Hepatotoxicity, Renal Toxicity, and Thrombocytopenia. Annex 4 - Specific adverse drug reaction follow-up forms updated to include: Questionnaires on Thrombocytopenia, Hepatotoxicity, Renal Toxicity.
0.5	RMP section SVII 1.2 Missing information – Long Term Safety, was updated to remove hepatotoxicity, renal toxicity and thrombocytopenia. RMP section III.1 Routine pharmacovigilance activities was updated to delete reference to the Annex 4 on targeted follow-up questionnaires. Summary RMP section II.B was updated to include Summary of important identified and potential risks.

Annex 4 – Specific adverse drug reaction follow-up forms

None

Annex 6 – Details of proposed additional risk minimisation activities

None proposed.

Version:	1
Version Date:	21 Jul 2025
Title:	open to respond to D195 Questions

APPROVALS:

Edel Mulligan, [redacted]