25 July 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Tryngolza (olezarsen sodium)
Treatment of familial chylomicronemia syndrome
EU/3/24/2973

Sponsor: Ionis Ireland Limited

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Olezarsen sodium
Other name(s)	ISIS 678354 sodium salt AKCEA-APOCIII-LRx, sodium salt 2'-O-(2 methoxyethyl) chimeric second-generation antisense oligonucleotide designed to bind to the human apoC-III messenger ribonucleic acid, sodium salt
International Non-Proprietary Name	Olezarsen sodium
Tradename	Tryngolza
Orphan condition	Treatment of familial chylomicronemia syndrome
Sponsor's details:	Ionis Ireland Limited Saint James House 72 Adelaide Road Dublin 2 D02 Y017 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Ionis Ireland Limited
COMP opinion	18 July 2024
EC decision	21 August 2024
EC registration number	EU/3/24/2973
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Larisa Gorobets / Paolo Gasparini
Applicant	Ionis Ireland Limited
Application submission	29 July 2024
Procedure start	15 August 2024
Procedure number	EMEA/H/C/006477
Invented name	Tryngolza
Therapeutic indication	Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS). Further information on Tryngolza can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/tryngolza
CHMP opinion	24 July 2025

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Joao Rocha
Sponsor's report submission	19 March 2025
COMP discussion	10-12 June 2025
COMP opinion (adoption via written procedure)	25 July 2025

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal designation in 2024 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing olezarsen sodium was considered justified based on preliminary clinical data showing an improvement in triglyceride levels and a reduction in acute pancreatitis attacks;
- the condition is life threatening and chronically debilitating due to recurrent episodes of pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus;
- the condition was estimated to be affecting approximately 0.13 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing olezarsen sodium will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product can be used in patients who cannot be treated with the only authorised medicine due to low platelet counts. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing olezarsen sodium as an orphan medicinal product for the orphan condition: treatment of familial chylomicronemia syndrome".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Familial chylomicronemia syndrome (FCS) is a rare genetic (autosomal recessive) hyperlipidaemia characterized by extremely high levels of triglycerides (TG) due to impaired clearance of chylomicrons from the blood. Clinical manifestations include abdominal pain, nausea, fatigue, diarrhoea, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis and failure to thrive. FCS often leads to recurrent episodes of acute pancreatitis, which can be life-threatening. Even though symptoms may start in childhood a diagnosis of FCS is usually later established in early adulthood, possibly due to under-recognition.

Thus far, mutations in six genes (LPL, apoC2, apoA5, LMF1, GPIHBP1, and GPD1) with monogenic effects and which are all implicated in lipoprotein lipase activity and have been recognized to lead to severe elevation of serum TGs due to disruption of the chylomicron removal pathways. Of those, the most frequently observed ones are homozygous or compound heterozygous mutations in the lipoprotein lipase (LPL) gene leading to non-function or very low function of LPL. The profound defect in the catabolism of chylomicrons and Very Low-Density Lipoprotein (VLDL) results in chylomicronaemia and TG levels >11.2 mmol/L (>1000 mg/dL). According to the latest ESC/EAS Guidelines for the management of dyslipidaemias (Mach et al., 2019), the risk of pancreatitis is clinically significant if TGs are >10 mmol/L (880 mg/dL), particularly when occurring in association with familial chylomicronaemia, and actions to prevent acute pancreatitis are mandatory. Notably, hypertriglyceridaemia is the cause of ~10% of all cases with pancreatitis, and patients can develop pancreatitis even when their TG concentration is 5–10 mmol/L (440–880 mg/dL).

The approved therapeutic indication "*Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS)*" falls within the scope of the designated orphan condition "treatment of familial chylomicronemia syndrome".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Episodes of acute pancreatitis is the most serious complication associated with familial chylomicronaemia syndrome and can be life threatening. Repeated episodes of acute pancreatitis can lead to pancreatic failure resulting in malabsorption and diabetes mellitus. Hypertriglyceridemia can cause significant cardiovascular disease. Hypertriglyceridemic pancreatitis is associated with significant morbidity and mortality.

The COMP has previously considered this condition to be both, life threatening and chronically debilitating, due to recurrent episodes of pancreatitis which may lead to pancreatic insufficiency

resulting in malabsorption, failure to thrive and diabetes mellitus. This view is maintained by the COMP, despite the availability of treatment options like volanesorsen.

Number of people affected or at risk

The sponsor proposes that the prevalence of FCS is around 0.02 per 10,000 persons.

This estimate is based on the epidemiologic data reported by Nierman and coworkers in 2005 (Nierman et al. 2005). This study captured all FCS patients with LPL deficiency in the Netherlands. As a result, the prevalence of FCS in the Netherlands was estimated as 0.02 per 10,000 (2:1,000,000) (Nierman et al. 2005).

In addition, the sponsor lists two studies which are based on retrospective analysis of patient records. In consequence, the source population in these studies is not the general population but information of subjects that were visiting a hospital and hence may overestimate the actual prevalence since the majority of the healthy population is excluded.

- In a study in Hungary, (Németh et al. 2022) FCS patients were identified using either the FCS score proposed by Moulin (Moulin et al. 2018) or with data mining, using medical records from 2 major Hungarian hospitals obtained during the period January 2007 to December 2014. Medical records of 1,342,124 patients were analysed and the FCS score of each patient was calculated. Machine learning models were trained based on the data of previously diagnosed FCS patients to identify other features that may improve FCS score calculation. This approach resulted in the identification of a total of 26 FCS patients and hence the estimated prevalence of FCS was 0.19 per 10,000 (19.4 in 1,000,000).
- Medical records of Italian adults from of the Niguarda Hospital were queried, covering the time period January 2016 to December 2018 (Pavanello et al. 2022). After the exclusion of secondary causes of hypertriglyceridemia (diabetes, alcohol misuse, etc.) and responses to lipid-lowering treatment probable FCS patients were identified. FCS was clinically defined in 8 subjects out of 143,615 charts queried through FCS Score calculation. Patients with a differential diagnose with FCS were identified and underwent a clinical, biochemical, and genetic evaluation. Molecular analysis of candidate genes confirmed FCS diagnosis in 5 patients (4 for mutations in LPL and 1 for GPIHBP1). Carriers of FCS causative mutations had higher TG levels and higher frequency of pancreatitis compared to non-genetic hypertriglyceridemia. Based on this information a prevalence of 0.6 per 10,000 was estimated (0.006%).

The sponsor concludes that the most accurate prevalence estimate for genetically identified FCS in the EU that could be identified from the scientific literature is 0.02 per 10,000 in the Netherlands. This is well below the criterion of an orphan disease in the EU of a prevalence of less than 5/10,000, and hence it appears safe to conclude from these data that FCS fulfils the epidemiological criterion of an orphan disease, even if there may be some variability between member states. This conclusion is supported by the two studies from Italy and Hungary that are based on patient records and hence have the fundamental methodological issue that they do not provide information on prevalence in the general population but in hospital patients.

The COMP pointed out that the sponsor's proposed estimate is lower than previously accepted values for this condition. For example, during the orphan maintenance procedure for Waylivra in 2019 the COMP agreed on a prevalence estimate of FCS of approximately 0.1 per 10,000 persons. Also, during the recent initial orphan designation of Tryngolza in July 2024 the COMP accepted a prevalence estimate of FCS of approximately 0.13 per 10,000 persons. During this procedure it had been pointed out that the prevalence of the familial form of chylomicronemia appears to have changed over time,

especially when considering the more recent studies which base their estimates on clinical rather than genetic criteria. Scientific literature has recently reported higher estimates. Overall, literature suggests a prevalence of approximately 4 to 13 in 1,000,000 as a valid estimate of patients suffering from clinical conditions suggestive of an FCS diagnosis (Khavandi et al. 2018; Pallazola et al., 2019). In the study by Pallazola et al. (2019), the authors retrospectively reviewed 1,627,763 patients seen at Johns Hopkins Hospital in the US from 2013-2017 and identified those who met clinical diagnostic criteria for FCS. FCS prevalence was 13 in 1,000,000 (95% CI: 8-20), demonstrating an FCS prevalence of 13-fold higher than previously described estimates. This is similar to the studies in the EU following the same approach (0.19 and 0.6 per 10,000). While these studies may overestimate the actual prevalence of FCS in the general population, the consistency in data between the EU and the USA indicates that extrapolation is feasible.

Considering the above, the COMP decided to maintain the more recently agreed prevalence values for FCS of approximately 0.1 per 10,000 persons, acknowledging that there remains some uncertainty due to the limited epidemiologic data in the EU of genetically confirmed cases.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

According to the latest ESC/EAS Guidelines for the management of dyslipidaemias (Mach et al., 2019), the mainstay of FCS management is extreme dietary fat restriction and abstinence of alcohol. The fat-restricted diet is usually not sufficient to obtain normal plasma levels of Triglycerides and Very Low-Density Lipoprotein. Available off-label treatment options to lower triglycerides are fibrates and omega-3 fatty acids, but response is usually limited. Lomitapide (off-label) may also be considered in severe cases. In the acute setting, plasmapheresis is able to rapidly lower TG levels.

At time of orphan maintenance, the satisfactory methods are established based on the therapeutic indication of the new vs the authorized therapies in a given condition, according to section 4.1 of the respective SmPC's. As mentioned above, the therapeutic indication is "Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS)."

At present there is only one medicinal product in the EU which is specifically authorized for the treatment of familial chylomicronemia syndrome, i.e. Waylivra (volanesorsen). As Tryngolza (olezarsen), Waylivra (volanesorsen) is an antisense oligonucleotide (ASO) designed to inhibit the formation of Apolipoprotein C-III (ApoC-III). ApoC-III is primarily secreted by the liver and small intestine and is found on triglyceride-rich lipoproteins such as chylomicrons, very low-density lipoprotein (VLDL), and remnant cholesterol. In contrast to Waylivra, Tryngolza is covalently bound to Trisaccharide of N-Acetylgalactosamine (GalNAc3), which enhances the drug's uptake by liver cells. Tryngolza achieves pharmacologic activity at lower doses as compared to Waylivra, owing to the GalNAc3 conjugation. Once Tryngolza is taken up in tissue, the conjugate is metabolized, liberating the active apo-C-III antisense compound, resulting in a reduction of apoC-III protein in plasma and increased clearance of Triglycerides/Very Low-Density Lipoprotein. Waylivra is administered subcutaneously once weekly for 3 months and subsequently reduced to once every 2 weeks. Tryngolza is also administered subcutaneously but only once per month.

The 4.1 Therapeutic indication of Waylivra, according to the SmPC reads as follows: "*Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate*".

Considering the above, in comparison to Waylivra, Tryngolza has no restriction for use in patients at high risk for pancreatitis, nor in those that failed diet and triglyceride lowering therapy.

The reasons for the restricted indication for Waylivra is the potential risk of thrombocytopenia of this product. According to the SmPC section 4.3, Waylivra is contra-indicated for patients with chronic or unexplained thrombocytopenia, and treatment should not be initiated in patients with thrombocytopenia (platelet count < 140 x 10E9 /L). Such contra-indications have not been established for Tryngolza.

This means that Tryngolza covers a broader FCS patient population as compared to Waylivra. Consequently, Waylivra is not considered to be a satisfactory method, for the purpose of this procedure.

Significant benefit

Not applicable.

4. COMP position adopted on 25 July 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of familial chylomicronemia syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.1 per 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to acute and chronic pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Tryngolza.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Tryngolza, olezarsen sodium, for treatment of familial chylomicronemia syndrome (EU/3/24/2973) is not removed from the Community Register of Orphan Medicinal Products.