24 April 2026
EMA/OD/0000258871
EMADOC-1700519818-3109082
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Redemplo (Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues)
Treatment of familial chylomicronaemia syndrome
EU/3/21/2459

Sponsor: Arrowhead Pharmaceuticals 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)	Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues
Other name(s)	Redemplo, Plozasiran,
International Non-Proprietary Name	Plozasiran
Tradename	Redemplo
Orphan condition	Treatment of familial chylomicronaemia syndrome
Sponsor's details:	Arrowhead Pharmaceuticals Ireland Limited One Spencer Dock North Wall Quay Dublin 1 D01 X9R7 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharma Gateway AB
COMP opinion	17 June 2021
EC decision	19 July 2021
EC registration number	EU/3/21/2459
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pharma Gateway AB to Arrowhead Pharmaceuticals Ireland Limited – EC decision of 30 January 2025
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Patrick Vrijlandt / Ewa Balkowiec Iskra
Applicant	Arrowhead Pharmaceuticals Ireland Limited
Application submission	28 February 2025
Procedure start	20 March 2025
Procedure number	EMA/H/C/006579/0000
Invented name	Redemplo
Therapeutic indication	Redemplo is indicated as an adjunct to diet to reduce triglyceride levels in patients with familial chylomicronemia syndrome (FCS). Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Redemplo
CHMP opinion	23 April 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook /Joao Rocha
Sponsor's report submission	01 April 2025

COMP discussion	14-16 April 2026
COMP opinion (adoption via written procedure)	24 April 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2021 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on clinical data demonstrating clinically relevant reductions in triglycerides in treated patients;
- 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 0.2 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 Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product used at low dose induced lasting and clinically relevant effect by lowering triglyceride levels in patients. This compared favourably to the existing antisense therapy which has to be used at a higher dose and more frequently. The Committee considered that this constitutes a clinically relevant advantage and major contribution to patient care.

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 Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues as an orphan medicinal product for the orphan condition: treatment of familial chylomicronaemia 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 is an autosomal recessive disorder caused by reduced lipoprotein lipase (LPL) function, an essential enzyme in the hydrolysis of plasma triglyceride. This results in hypertriglyceridemia and accumulation of chylomicrons in plasma, often leading to acute pancreatitis.

Most cases (>90%) are attributed to loss of function mutations in the LPL gene itself, resulting in severely impaired or absent LPL activity. More rarely, FCS is due to biallelic mutations in other genes encoding for the LPL cofactors apolipoproteins C2 and A5 (APOC2 and APOA5), or other proteins that are required for LPL activity, including glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1), and lipase maturation factor 1 (LMF1).

The FCS phenotype is characterised by elevated chylomicrons (CMs). Patients often present in the neonatal period/early infancy, especially individuals carrying *LPL* mutations, and typically occurs before reaching adulthood. However, disease onset may be delayed into late adulthood in patients homozygous for the non-*LPL* disease causing mutations.

The most severe complication of FCS is acute pancreatitis (AP), which is commonly recurrent, and may lead to permanent exocrine or endocrine insufficiency, and is potentially fatal (Gaudet 2016; Davidson 2017).

A panel of European experts provided guidance developed an algorithm-based diagnosis tool for identification of these patients (Moulin at al. Atherosclerosis; Volume 275, August 2018, Pages 265-272); Features included in this FCS score comprise: severe elevation of plasma triglycerides (fasting TG levels >10mmol/L [885 mg/dL] on multiple occasions), refractory to standard TG-lowering therapies, a young age at onset, the lack of secondary factors (except for pregnancy and oral oestrogens) and a history of episodes of acute pancreatitis.

A definitive diagnosis can be further confirmed via genetic testing.

The approved therapeutic indication "*Redemplo is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with familial chylomicronaemia syndrome (FCS) in whom response to diet and triglyceride lowering therapy has been inadequate. See section 4.2 for patient selection criteria"* falls within the scope of the designated orphan condition "Treatment of familial chylomicronaemia 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 are 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, and severe abdominal pain. Hypertriglyceridemic pancreatitis is associated with significant morbidity and mortality.

Patients may also exhibit eruptive xanthoma on the trunk or extremities (<50% of patients), lipaemia retinalis, hepatosplenomegaly due to infiltration of macrophages in response to CM deposition (Stroes 2017). A range of cognitive and emotional symptoms often described as "mental fog" are reported, e.g. difficultly concentrating, forgetfulness, impaired judgement, anxiety/fear/worry and a feeling of loss of control/powerlessness (Davidson 2017; Blom 2018; Moulin 2018). Reduced quality of life is common, and associated with the disease manifestations, the requirement to follow a strict diet devoid of almost all dietary fat and carbohydrates, and lifestyle changes imposed by this condition.

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.

Number of people affected or at risk

In the original orphan designation (EU/3/21/2459), from July 2021, a prevalence estimate of 0.2 in 10,000 persons was accepted by the COMP. This estimate was based on a comprehensive global review of primary epidemiologic data for FCS, see summarized in Table 1. No reports directly informing the prevalence of FCS in the EU were identified in the original designation searches.

For the purpose of the review of the orphan criteria, the sponsor has conducted a gap analysis of additional epidemiologic data which has been published since the time of orphan designation.
The sponsor identified one additional relevant publication that reported an estimate for the prevalence of FCS (genetically confirmed and clinical combined) *in central Europe* (Hungary) (Németh 2022). The study by Németh 2022 aimed to determine the prevalence of FCS in central Europe based on classification of a large number of patients by likelihood of having FCS, using the scoring system proposed by Moulin 2018. In total, FCS scores were calculated for 1,341,722 individuals who visited the two major healthcare providers in the Northern Great Plain region of Hungary. Among these patients, a total of 26 had an FCS score ≥10, so were very likely to have genetic FCS. The authors reported that this translated into a prevalence estimate of 19.4 per million, ie, 0.19 per 10,000. This value is very similar to the prevalence estimate accepted by the COMP at time of orphan designation.

Table 1. Prevalence of FCS in the general population up until orphan designation (2021)

Source	Country	Prevalence (per 10,000)
Tripathi 2021	US (California)	0.0026-0.0066/10,000 0.18/10,000
Warden 2020	US (Oregon)	0.01-0.02/10,000 [0.36/10,000] [0.83/10,000]
Pallazola 2020	US (Maryland)	0.13/10,000 (95% CI 8-20)
Patni 2018 Ahmad 2014	US (Texas)	6/1.79 million = 0.03/10,000 paediatric persons
Rengarajan 2018	US (Texas)	0.8/10,000
Khavandi 2018	US (rural update New York)	0.10/10,000
Ariza 2018	Spain	N/A
Dron 2019	Canada and US	Rate applied to prevalence of SHTG in general population in US (1 in 600): 0.18/10,000 Rate applied to prevalence of SHTG in general population in Norway (1 in 1000): 0.14/10,000
Tada 2015	Japan	0.57/10,000
Gagné 1989	Canada (Quebec)	Charlevoix: 2/10,000 Saguenay-lac St Jean: 0.97/10,000 Quebec city: 0.19/10,000 Other: <0.01/10,000 Note this population has a founder effect.

Abbreviation: eHTG = extreme hypertriglyceridaemia (≥ 2000 mg/dL).

In conclusion, considering the previously reviewed epidemiologic data at time of orphan designation as well as the newly identified prevalence estimate for an EU country, the COMP accepted a prevalence of FCS of less than 0.2 in 10,000 persons. Accordingly, FCS remains an orphan condition with respect to the prevalence criterion defined in Article 3 of Regulation (EC) 141/2000, the Orphan regulation.

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

Current standard of care are dietary restrictions of fat and carbohydrates, and life-style interventions are avoiding alcohol. But it has been described that adherence to the fat-restricted diet does not mitigate the hyper-TG and high risk of pancreatitis sufficiently in many patients (Williams et al., 2018).

Conventional lipid-lowering therapies (fibrates, statins) are often tried, but these are poorly effective in FCS as their action requires normal LPL. Effectiveness of omega-3 fatty acids, routinely used in pharmacologic doses for treatment of other types of severe hypertriglyceridemia, has been inconsistent in patients with FCS (Williams et al., Journal of Clinical Lipidology

Volume 12, Issue 4, July–August 2018, Pages 908-919).

Two medicinal products are currently authorized in the EU for the treatment of FCS: Waylivra (volanesorsen) and, more recently, Tryngolza (Olezarsen), (Table 2).

Table 2. Authorized medicinal products for FCS in the EU and Satisfactory Methods vis a vis Redemplo

Authorized Product for FCS	**4.1 Therapeutic Indication**	**Satisfactory Method vis a vis Redemplo**
Redemplo (Plozasiran)	**Redemplo** is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with familial chylomicronaemia syndrome (FCS) in whom response to diet and triglyceride lowering therapy has been inadequate See section 4.2 for patient selection criteria	n/a
Waylivra (Volanesorsen)	**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.	**No** -> Redemplo has no restriction for use in patients without genetically confirmed FCS or patients with a at high risk for pancreatitis
Tryngolza (Olezarsen)	**Tryngolza** is indicated as an adjunct to diet in adult patients for the treatment **of genetically confirmed** familial chylomicronemia syndrome (FCS).	**No** -> Redemplo has no restriction for use in patients without genetically confirmed FCS

The COMP considers that neither of the two medicinal products currently authorized in the EU for the treatment of FCS (Waylivra and Tryngolza) are satisfactory methods, for the purpose of this maintenance of the orphan designation procedure. Based on the 4.1 therapeutic indications of the respective SmPC's, Redemplo may be used in a broader patient population, i.e. including patients not at a high risk for pancreatitis (as for Waylivra) and/or with a clinical FCS diagnosis. The therapeutic indications of both Waylivra and Tryngolza are restricted to genetically confirmed FCS.

In section 4.2 of the SmPC of Redemplo, the criteria for patient selection are described as follows: "**When considering the use of Redemplo, it is important that FCS diagnosis of a patient is established by either genetic testing, or by the presence of the following clinical criteria: fasting triglyceride levels ≥ 10 mmol/L (≥ 880 mg/dL) that are refractory to standard lipid-lowering therapy and at least one of the following: prior history of acute pancreatitis not caused by alcohol or cholelithiasis, history of recurrent hospitalisations for severe abdominal pain without other explainable cause, history of childhood pancreatitis, or family history of hypertriglyceridaemia-induced pancreatitis.* "

Significant benefit

Not applicable.

4. COMP position adopted on 24 April 2026

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 chylomicronaemia syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.2 in 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 authorized in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Redemplo.

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 Redemplo, (synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, Plozasiran) for treatment of familial chylomicronaemia syndrome (EU/3/21/2459) is not removed from the Community Register of Orphan Medicinal Products.