Health Technology Briefing
January 2024

Olezarsen for treating familial chylomicronaemia syndrome

Company/Developer	Ionis Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34563	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Olezarsen is in clinical development for the treatment of patients with familial chylomicronaemia syndrome (FCS). FCS is a rare genetic disorder that causes very high levels of triglycerides, which is a kind of fat, in the blood. This can lead to serious health problems, including acute and chronic pancreatitis and type 3c diabetes. Symptoms of this disorder include moderate to severe abdominal pain, unpredictable and recurrent episodes of acute pancreatitis, liver and spleen enlargement, reduced cognition, and fatigue. Current treatment options are limited, and an extremely restrictive, very low-fat diet is critical to help manage symptoms. This can be very challenging for patients, and often, many still have high triglyceride levels even when the diet is closely followed. Despite best intentions, patients, clinicians, and caregivers struggle with dietary control, and the risk of adverse consequences of raised triglycerides remains.

Olezarsen is a medicinal product designed to block the production of apoC-III (a protein produced in the liver that slows the breakdown of fats in the blood) and lower its concentrations to treat people with FCS. Olezarsen may allow fewer dose administration, with each dose being much smaller, and still have the effects last longer compared to the usual treatment. If licensed, olezarsen will offer a new treatment option for patients with FCS.

Proposed Indication

For the treatment of familial chylomicronaemia syndrome (FCS) in patients aged 18 years and older who have a history of pancreatitis.[1]

Technology

Description

Olezarsen is an N-acetylgalactosamine-(GalNac) conjugated antisense oligonucleotide (ASO) that uses ligand-conjugated antisense (LICA) technology.[2,3] It is designed to inhibit the production of apoC-III for patients who are at risk of disease due to elevated triglyceride levels, including those with FCS.[4] ApoC-III is a protein produced in the liver that regulates triglyceride metabolism in the blood.[2,5]

Olezarsen is in clinical development for the treatment of FCS. In the phase III clinical trial (BALANCE; NCT04568434) olezarsen was administered once every 4 weeks by subcutaneous (SC) injection for 53 weeks with a 13 week follow-up period.[1] At the end of the study (53 weeks), patients had the option to enter an open-label extension study (NCT05130450), for an additional 201 weeks which included an up to 31-day qualification period, a 157-week treatment period, and also a 13-week post-treatment evaluation period.[6]

Key Innovation

Current treatment options for people with FCS are limited. The initial supportive treatment option is centred around dietary changes. This is highly restrictive and can be very challenging for patients, particularly if diabetes develops. Also, people often still have high triglyceride levels even when the diet is closely followed.[7] Olezarsen is a GalNAc-conjugated ASO that targets selectively the hepatic synthesis of apoC-III. The GalNAc moiety and linker of olezarsen's nucleic acid ensure less frequent administration of significantly lower doses for a longer duration of action compared to standard of care.[8] Studies have found that olezarsen treatment improved the lipoprotein profile and reduced atherogenic lipoproteins.[3,9] If licensed, olezarsen will offer a new treatment option for patients with FCS.

GalNac3-conjugated ASOs, in comparison to unconjugated ASOs, are designed to allow for: increased targeting of the drug to the desired tissue and cell type, reduced injection volumes due to 20 to 30-fold increase in potency, and potential for lower, less-frequent dosing based on investigational studies.[9-14]

Regulatory & Development Status

Olezarsen does not currently have Marketing Authorisation in the EU/UK for any indication.

Olezarsen received an FDA Fast Track designation in January 2023 for the treatment of FCS.[5]

Olezarsen is currently in phase II/III clinical development for the treatment of FCS and severe hypertriglyceridemia.[15]

Patient Group

Disease Area and Clinical Need

FCS is a rare genetic metabolic disorder of lipid metabolism caused by homozygous mutations in the lipoprotein lipase gene. It is characterised by high levels of triglycerides in the plasma and a build-up of

chylomicrons (the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body).[7] FCS follows an autosomal recessive (biallelic) pattern of inheritance; in most cases (~90%), monogenic mutations have been found in the lipoprotein lipase (LPL) gene itself.[16,17] In cases without a LPL gene mutation, affected genes include those coding for apolipoprotein C-II, apolipoprotein A-V, lipase maturation factor-1, or glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), which are involved in LPL transport and/or function.[18] Symptoms include repeated episodes of severe abdominal pain, unpredictable and recurrent episodes of acute pancreatitis, liver and spleen enlargement, and fatigue. Acute pancreatitis is a life-threatening condition for which intensive care may be needed. Repeated attacks of acute pancreatitis may lead to chronic pancreatitis. Pancreatic damage and type 3c diabetes can develop as a result of pancreatitis and often makes FCS more difficult to manage.[7] In addition, people with FCS are often unable to work, and the condition affects a patient's independence, adding to their disease burden.[5,7] In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection, and cyst formation, as well as damage to other vital organs such as the heart, lungs, and kidneys.[5]

The prevalence of FCS is estimated to be 1 to 2 per million people, which equates to about 55 to 110 people in England.[7] In England 2022-23, there was 1 finished consultant episode (FCE) and 1 admission for hyperchylomicronaemia (ICD-10 code E78.3). This resulted in 0 FCE bed days and 1 day case.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommend volanesorsen for treating FCS in patients who are genetically-confirmed and at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate.[7]

To keep plasma triglyceride levels low, management consists of severely restricting dietary fat intake (usually to between 10 g and 20 g daily, about a quarter of the normal daily intake suggested for an adult) and consuming no alcohol. People with the condition may take several drugs to control pain and other symptoms of FCS, including corticosteroids, analgesics, anxiolytics, antidepressants, diabetes treatments and antithrombotic drugs. Due to maintaining a fat-restricted diet, there is also the need to supplement essential fatty acids (linoleic and alpha linolenic acids) and fat-soluble vitamins (vitamins A, D, E and K). In addition, treatments for hypercholesterolaemia (such as fibrates, nicotinic acids, and statins) may be prescribed but are of limited value.[7]

Clinical Trial Information

Trial	**BALANCE; NCT04568434, EudraCT 2021-002536-67;** A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRX Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS) **Phase III** – Completed **Location(s)**: 9 EU countries, UK, USA, and other countries **Primary completion date**: July 2023
Trial Design	Randomized, double-blinded, parallel assignment
Population	N=66 (actual); patients aged 18 years and older with diagnosed FCS
Intervention(s)	Olezarsen was administered once every 4 weeks by subcutaneous (SC) injection for 53 weeks with a 13-week follow-up period

Comparator(s)	Placebo
Outcome(s)	**Primary outcome measure:** • Percent Change from Baseline in Fasting TG at 6 Months (average of Weeks 23, 25, and 27) compared to placebo [time frame: Baseline and Month 6 See trial record for full list of other outcomes.
Results (efficacy)	The trial met its primary efficacy endpoint with a statistically significant reduction in triglyceride (TG) levels with the olezarsen 80 mg monthly dose at six months compared to placebo (p=0.0009); triglyceride lowering continued to improve at 12 months. In addition, olezarsen 80 mg showed a 100 percent reduction in acute pancreatitis events compared to placebo (0 events for olezarsen versus 11 events for placebo), a key secondary endpoint.[4] Treatment with olezarsen 80 mg resulted in a >75% reduction in apoC-III, a protein produced in the liver that regulates TG metabolism in the blood. In addition to the 80 mg monthly dose, the study also evaluated a lower 50 mg monthly dose. Olezarsen demonstrated a dose-dependent effect, with both study doses showing a substantial reduction in pancreatitis. The lower 50 mg dose did not reach statistical significance at six months on the primary endpoint of triglyceride lowering (p=0.0775).[4]
Results (safety)	Olezarsen demonstrated a favourable safety and tolerability profile in the study. There were more adverse events in the placebo group compared to the olezarsen groups, primarily due to pancreatitis events. The majority of adverse events in the olezarsen groups were mild in severity. There was a low incidence of injection site reactions. No hepatic or renal toxicity events occurred and there were no clinically meaningful platelet reductions. One death was reported in the study, which was deemed as not related to study drug.[4]

Clinical Trial Information	
Trial	NCT05130450, **EudraCT** 2021-003280-95; An Open-Label Extension Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS) **Phase III** – Active, not recruiting **Location(s)**: 8 EU countries, UK, USA, and Canada **Primary completion date**: January 2025
Trial Design	Open label, single group assignment
Population	N=60 (actual); patients aged 18 years and older with diagnosed FCS who participated in trial NCT04568434
Intervention(s)	Olezarsen administered once every 4 weeks by subcutaneous (SC) injection from Week 1 through Week 153.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure:

	• Percent Change From Baseline in Fasting TG at 6 Months (Average of Weeks 23, 25, and 27) Compared to Baseline [time frame: Baseline and 6 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT05185843, **EudraCT** 2021-003635-29; An Open-Label Safety Study of AKCEA-APOCIII-LRX Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS) Previously Treated With Volanesorsen (ISIS 304801) **Phase III** – Active, not recruiting **Location(s)**: USA, Canada, and Sweden **Primary completion date**: March 2025
Trial Design	Open label, single group assignment
Population	N=24 (actual); patients aged 18 years and older with diagnosed FCS who are currently on or previously treated with volanesorsen
Intervention(s)	Olezarsen administered once every 4 weeks by subcutaneous (SC) injection for up to 153 weeks
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Proportion of Participants with Decrease in Platelet Count by >30% or >50%, or With Platelet Count Value <50,000/cubic millimetre (mm^3) [time frame: Baseline to week 157] • Proportion of Participants with Major or Clinically Relevant Non-major Bleeding Events [time frame: Baseline to week 157] • Proportion of Participants with Decrease in Estimated Glomerular Filtration Rate (eGFR) by >30% or >50% [time frame: Baseline to week 157] • Proportion of Participants with Urine Protein/Creatinine Ratio (UPCR) ≥1000 milligram (mg)/gram (g) or with Urine/Albumin Creatinine Ratio (UACR) ≥500 mg/g [time frame: Baseline to week 157] • Proportion of Participants With Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) >5 x Upper Limit of Normal (ULN) [time frame: Baseline to week 157] • Proportion of Participants With ALT or AST >3 x ULN and Total Bilirubin > 2 x ULN [time frame: Baseline to week 157] • Proportion of Participants With Total Bilirubin >2 mg/decilitre (dL) [time frame: Baseline to week 157] See trial record for full list of other outcomes.
Results (efficacy)	-

Results (safety)	-

Estimated Cost

The cost of olezarsen is not yet known.

Relevant Guidance

NICE Guidance

- NICE highly specialised technologies guidance. Volanesorsen for treating familial chylomicronaemia syndrome (HST13). October 2020.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.

Other Guidance

- Ronald B. Goldberg and Alan Chait. A Comprehensive Update on the Chylomicronemia Syndrome. October 2020.[20]
- James M. Falco. Familial Chylomicronemia Syndrome: A Clinical Guide for Endocrinologists. August 2018.[21]

Additional Information

Ionis Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS). Trial ID: NCT04568434*. 2020. Status: Completed. Available from: https://clinicaltrials.gov/study/NCT04568434 [Accessed 14 December 2023].

2 Ionis Pharmaceuticals Inc. *Ionis initiates pivotal Phase 3 clinical study of olezarsen in patients with severe hypertriglyceridemia*. Press release 2 November 2021. Available from: https://ir.ionispharma.com/news-releases/news-release-details/ionis-initiates-pivotal-phase-3-clinical-study-olezarsen [Accessed 6 November 2023].

3 Shamsudeen I, Hegele RA. Safety and efficacy of therapies for chylomicronemia. *Expert Review of Clinical Pharmacology*. 2022;15(4):395-405. Available from: https://doi.org/10.1080/17512433.2022.2094768.

4 Ionis Pharmaceuticals Inc. *Ionis announces positive olezarsen topline results from Phase 3 study in people with familial chylomicronemia syndrome*. Press release 26 September 2023. Available from: https://ir.ionispharma.com/news-releases/news-release-details/ionis-announces-positive-olezarsen-topline-results-phase-3-study [Accessed 23 November 2023].

5 Ionis Pharmaceuticals Inc. *Ionis receives FDA Fast Track designation for olezarsen in patients with familial chylomicronemia syndrome*. Press release 31 January 2023. Available from: https://ir.ionispharma.com/news-releases/news-release-details/ionis-receives-fda-fast-track-designation-olezarsen-patients [Accessed 6 November 2023].

6 ClinicalTrials.gov. *An Open-Label Extension Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)*. *Trial ID: NCT05130450*. 2021. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/study/NCT05130450 [Accessed 22 December 2023].

7 National Institute for Health and Care Excellence (NICE). *Volanesorsen for treating familial chylomicronaemia syndrome* (*HST13)*. Available from: https://www.nice.org.uk/guidance/hst13/resources/volanesorsen-for-treating-familial-chylomicronaemia-syndrome-pdf-50216257168837 [Accessed 6 November 2023].

8 Packard CJ, Pirillo A, Tsimikas S, Ference BA, Catapano AL. Exploring apolipoprotein C-III: pathophysiological and pharmacological relevance. *Cardiovascular Research*. 2023. Available from: https://doi.org/10.1093/cvr/cvad177.

9 Wang Y, Yu RZ, Henry S, Geary RS. Pharmacokinetics and Clinical Pharmacology Considerations of GalNAc3-Conjugated Antisense Oligonucleotides. *Expert Opinion on Drug Metabolism & Toxicology*. 2019;15(6):475-85. Available from: https://doi.org/10.1080/17425255.2019.1621838.

10 Viney NJ, Guo S, Tai LJ, Baker BF, Aghajan M, Jung SW, et al. Ligand conjugated antisense oligonucleotide for the treatment of transthyretin amyloidosis: preclinical and phase 1 data. *ESC Heart Fail*. 2021;8(1):652-61. Available from: https://doi.org/10.1002/ehf2.13154.

11 Gaudet D, Karwatowska-Prokopczuk E, Baum SJ, Hurh E, Kingsbury J, Bartlett VJ, et al. Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. *European Heart Journal*. 2020;41(40):3936-45. Available from: https://doi.org/10.1093/eurheartj/ehaa689.

12 Tardif JC, Karwatowska-Prokopczuk E, Amour ES, Ballantyne CM, Shapiro MD, Moriarty PM, et al. Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridaemia and at high cardiovascular risk. *Eur Heart J*. 2022;43(14):1401-12. Available from: https://doi.org/10.1093/eurheartj/ehab820.

13 Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif J-C, Baum SJ, Steinhagen-Thiessen E, et al. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. *New England Journal of Medicine*. 2020;382(3):244-55. Available from: https://doi.org/10.1056/NEJMoa1905239.

14 Ferrone JD, Bhattacharjee G, Revenko AS, Zanardi TA, Warren MS, Derosier FJ, et al. IONIS-PKK(Rx) a Novel Antisense Inhibitor of Prekallikrein and Bradykinin Production. *Nucleic Acid Ther*. 2019;29(2):82-91. Available from: https://doi.org/10.1089/nat.2018.0754.

15 ClinicalTrials.gov. *8 Studies found for: olezarsen | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3*. Available from: https://classic.clinicaltrials.gov/ct2/results?term=olezarsen&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 6 November 2023].

16 Brahm AJ, Hegele RA. Chylomicronaemia - current diagnosis and future therapies. *Nature Reviews Endocrinology*. 2015;11(6):352-62. Available from: https://doi.org/10.1038/nrendo.2015.26.

17 Hegele RA, Berberich AJ, Ban MR, Wang J, Digenio A, Alexander VJ, et al. Clinical and biochemical features of different molecular etiologies of familial chylomicronemia. *Journal of Clinical Lipidology*. 2018;12(4):920-7.e4. Available from: https://doi.org/10.1016/j.jacl.2018.03.093.

18 Brown EE, Sturm AC, Cuchel M, Braun LT, Duell PB, Underberg JA, et al. Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. *Journal of Clinical Lipidology*. 2020;14(4):398-413. Available from: https://doi.org/10.1016/j.jacl.2020.04.011.

19 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23: Diagnosis*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 6 November 2023].

20 Goldberg RB, Chait A. A Comprehensive Update on the Chylomicronemia Syndrome. *Frontiers in Endocrinology*. 2020;11. Available from: https://doi.org/10.3389/fendo.2020.593931.

21 Falko JM. Familial Chylomicronemia Syndrome: A Clinical Guide for Endocrinologists. *Endocrine Practice*. 2018;24(8):756-63. Available from: https://doi.org/10.4158/EP-2018-0157.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.