Health Technology Briefing
July 2024

Lomitapide for treating homozygous familial hypercholesterolaemia in children aged 5 to 17 years

Company/Developer	Chiesi Limited

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30957	NICE ID: Not Available	UKPS ID: 674938

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Lomitapide is currently in clinical development for the treatment of paediatric patients with homozygous familial hypercholesteraemia (HoFH) receiving stable lipid-lowering therapy. HoFH is a more severe form of familial hypercholesterolaemia, a condition passed down through families, which raises blood low density lipoprotein (LDL) cholesterol to very high levels. Low density lipoprotein cholesterol (LDL-C) is often referred to as 'bad cholesterol'. Attempts to lower LDL-C levels often require multiple lipid-lowering drugs and LDL apheresis. Despite these therapies, most patients with HoFH do not reach guideline-recommended LDL-C levels.

Lomitapide blocks the action of microsomal triglyceride transfer protein (MTP) responsible for assembling fatty substances such as cholesterol and triglyceride into larger particles called lipoproteins, which are then released into the blood stream. Blocking this protein enables lomitapide to decrease the level of fats released into the blood, thereby helping to reduce the level of cholesterol in hypercholesterolaemia. Lomitapide, taken orally, will offer an additional treatment option for paediatric patients aged 5 to 17 years with HoFH.

Proposed Indication

Paediatric patients with homozygous familial hypercholesterolaemia (HoFH) on stable lipid lowering therapy.[1]

Technology

Description

Lomitapide (Lojuxta) is a low-density lipoprotein (LDL) receptor-independent lipid lowering therapy, and a selective inhibitor of microsomal triglyceride transfer protein (MTP), an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. MTP plays a key role in the assembly of apo B containing lipoproteins in the liver and intestine. Inhibition of MTP reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including LDL-cholesterol and triglycerides.[2]

Lomitapide is currently in clinical development for the treatment of paediatric patients with HoFH receiving stable lipid lowering therapies (LLTs).[1] In the ongoing phase III trial (NCT04681170), lomitapide is administered as oral capsules starting at 2mg per day in patients aged 5 to 15 years or 5 mg per day in patients aged 16 to ≤17 years at week 1. The dose is then up titrated (5 mg, 10 mg then 20 mg), based on LDL-cholesterol (LDL-C) levels, until patients are receiving the maximum tolerated dose of 20 mg (age 5 to 10 years), 40 mg (age 11 to 15 years), or 60 mg (age 16 to ≤17 years).[a,1]

Key Innovation

Attempts to lower LDL-C levels often require multiple lipid-lowering drugs and LDL apheresis. Despite these therapies, a majority of patients with this disorder do not reach guideline-recommended LDL-C levels.[3] Lomitapide treatment for up to 9 years (median 19 months) resulted in more than half attaining at least 50% reduction from baseline in LDL-C at last visit, with less need for apheresis in a substantial proportion of patients.[4] In children and adolescents, a LDL-C goal of <3 mmol/L (<115 mg/dL) is recommended if treatment is initiated before 18 years.[4] Without treatment, HoFH can lead to heart disease at a very young age, and deaths in patients with HoFH have been reported in patients under 5 years of age.[5]

If licensed, lomitapide would offer an additional, LDL-receptor-independent, treatment option for paediatric patients aged 5 to 17 years with HoFH patients.

Regulatory & Development Status

Lomitapide currently has Marketing Authorisation in the UK as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LDL apheresis in adult patients with HoFH.[2]

Lomitapide is currently not in clinical development for any other indications.[6]

Lomitapide has an EU orphan designation for the treatment of familial chylomicronemia.[7]

Patient Group

Disease Area and Clinical Need

[a] Information provided by Chiesi Limited – not confidential.

HoFH is a rare form of familial hypercholesterolaemia (FH), a genetic disease that raises the blood cholesterol to very high levels. HoFH is the more severe form that raises LDL-C (bad cholesterol) levels even higher.[8] The 2023 European Atherosclerosis Society (EAS) consensus statement proposes that HoFH should be suspected if untreated LDL-C levels are approximately greater than 400mg/dL.[4] Those living with HoFH have increased risk of coronary heart disease and are at risk for premature atherosclerotic disease and life-threatening cardiac events as early as their teen years.[9] Alongside increased LDL-C levels, patients can also present with xanthomas (skin lesions) on the skin, tendons and eyes.[10] Corneal arcus surrounding the entire inside edge of the cornea is often also present. Most individuals with HoFH experience severe coronary artery disease by their mid-20's if not aggressively treated. Narrowing of the heart valve leading to the aorta (aortic stenosis) often occurs, which may make it necessary to replace the aortic valve. Early intervention with effective lipid-lowering therapy is needed to reduce the likelihood of vascular events.[11]

Based on actual patient numbers being treated in major apheresis centres, it is estimated that the prevalence of HoFH may be 1 in 670,000 adults in England.[12] The incidence of HoFH has been estimated to be approximately one case per every 160,000 – 300,000 people.[13] In England (2022 – 23), there were 1,408 finished consultant episodes (FCEs) and 1,345 admissions for a primary diagnosis of pure hypercholesterolaemia or FH (ICD 10 code E78.0, of which HoFH patients make up 0.036%)[14,15] resulting in 1,144 day cases and 3,352 FCE bed days.[16]

Recommended Treatment Options

Lipid-modifying drug therapy, statins and specialist treatments like LDL-lowering apheresis are treatment options recommended by the National Institute for Health and Care Excellence (NICE) for children and young people with familial hypercholesteremia.[17]

Clinical Trial Information

Trial	NCT04681170, EudraCT 2019-002278-30; Phase III, single arm, open label, international, multi centre study to evaluate the efficacy and safety of lomitapide in paediatric patients with homozygous familial hypercholesterolaemia (HoFH) on stable lipid lowering therapy. **Phase III** – active, not recruiting **Location(s)** – 3 EU countries, Israel, Saudi Arabia, and Tunisia **Primary completion date**: October 2022
Trial Design	Non-randomised, parallel assignment, open label
Population	N = 46 (actual); paediatric patients with HoFH; aged 5 to 17 years.
Intervention(s)	Lomitapide 2mg, 5mg, 10mg and 20mg oral capsules (escalating dose to maximal allowable dose by week 16/20 based on patient age (5, 10 years, 11-15 years, and 16 to ≤17 years).
Comparator(s)	None
Outcome(s)	Primary outcome measures: • Efficacy endpoint percent changes in LDL-C • Safety endpoints adverse events (AE) reporting See trial record for full list of other outcomes.

Results (efficacy)	Primary endpoint of trial was met as clinically meaningful and statistically significant reductions from baseline in LDL-C at week 24 were observed. Overall, mean (SD) LDL-C decreased from 435.79 (189.46) mg/dL at baseline to 176.49 (90.40) mg/dL at week 24. Mean change from baseline was -53.53% (95% CI -61.62; -45.44), p<0.0001. 41.9% patients achieved European Atherosclerotic Society (EAS) 2023 target LDL-C levels at any time up to week 24 <135 mg/dL (3.5 mmol/L). In patients aged 5–10 years, mean (SD) LDL-C decreased from 538.51 (199.92) mg/dL at baseline to 207.24 (102.17) mg/dL at week 24. Mean change from baseline was -56.53% (95% CI -68.47; -44.59). In patients aged 11–17 years, mean (SD) LDL-C decreased from 346.47 (126.80) mg/dL at baseline to 149.75 (70.56) mg/dL at week 24. Mean change from baseline was -50.92% (95% CI -62.06; -39.79). Secondary endpoints examining other lipid markers also showed statistically significant reductions from baseline. Overall, mean (SD) non-HDL-C decreased from 454.13 (191.87) mg/dL at baseline to 184.68 (92.56) mg/dL at week 24. Mean change from baseline was -53.86% (95% CI -61.66; -46.05), P<0.0001. Overall, mean (SD) total cholesterol decreased from 485.53 (188.18) mg/dL at baseline to 217.40 (94.60) mg/dL at week 24. Mean change from baseline was -50.05% (95% CI -57.64; -42.45), p<0.0001. Overall, mean (SD) very low density lipoprotein cholesterol (VLDL-C) decreased from 18.33 (7.80) mg/dL at baseline to 8.30 (4.45) mg/dL at week 24. Mean change from baseline was -50.16% (95% CI -59.12; -41.21), p<0.0001. Over half of patients had >50% reductions in LDL-C, and the maximum reduction in an individual patient was 95%. Mean apolipoprotein B (ApoB) levels reduced from 316.6±133.0mg/dL to 132.7±63.2mg/dL over 24 weeks (–52.4%; p<0.0001). Similarly, lipoprotein (a) (Lp(a)) levels (units according to lab practice) reduced from 126.2±118.7nmol/L to 79.4±78.5nmol/L and 48.7±47.5mg/dL to 34.9±30.2mg/dL over 24 weeks (–23.6%; p=0.003; –11.3%; p=0.2884, respectively). For both parameters, subgroup analyses indicated consistency across age groups, LA, concomitant medications, history of cardiovascular disease, and dose reductions/interruptions.[b,18]
Results (safety)	40 of the 43 patients experienced an AE in the 24-week efficacy phase. Two patients withdrew due to AEs. The majority of patients experienced mild (48.8%) to moderate (30.2%) treatment emergent adverse effects (TEAEs). Five patients had serious AEs, with only one considered to be related to lomitapide. Five patients experienced six AEs of special interest (AESI) (11.6%); two events occurred in two patients aged 11 to 17 years (8.7%) and resulted in premature discontinuation of the study. Four events were reported for three patients aged 5 to 10 years (15.0%). All AESIs were assessed as being related to lomitapide treatment. The percentage of patients with elevations in aspartate aminotransferase (AST) was 23%, and in alanine aminotransferase (ALT) this was 28%. There were no clinically significant changes in growth (height, weight, body mass index) and maturation Z-scores at week 24 (safety analysis set). Most fat-soluble vitamins remained within normal ranges, except Vitamin E which was

[b] Information provided by Chiesi Limited – not confidential.

	higher than normal. Patients received vitamin E supplementation at a dose according to age. Vitamin E levels were elevated at baseline and decreased by week 24, as expected, but they remained above the upper limit of normal at week 24.[c]

Estimated Cost

The NHS indicative cost for lomitapide is £17,765 for a 28 pack of 5 or 10 or 20 mg capsules.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over (ID2704). Expected September 2024.
- NICE guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (NG238). December 2023.
- NICE clinical guidance. Familial hypercholesterolaemia: identification and management (CG71). October 2019.
- NICE quality standard. Cardiovascular risk assessment and lipid modification (QS100). September 2015.
- NICE quality standard. Familial hypercholesterolaemia (QS41). August 2013.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Lomitapide for treating homozygous familial hypercholesterolaemia (adults). 170059P. June 2018
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cardiology: Inherited Cardiac Conditions (All Ages). A09/S/c.
- NHS England. 2013/14. NHS Standard Contract for Metabolic Disorders (Laboratory Services). E06/S/c

Other Guidance

- Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. July 2023.[4]
- McErlean S, Mbakaya B, and Kennedy C. Familial Hypercholesterolaemia. July 2023.[20]
- Lui DTW, Lee ACH, Tan KCB. Management of Familial Hypercholesterolemia: Current Status and Future Perspectives. January 2021.[21]
- McGowan MP, Dehkordi SHH, Moriarty PM, and Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. December 2019.[22]
- Public Health England. Familial Hypercholesterolaemia. Implementing a systems approach to detection and management. March 2018.[23]

Additional Information

[c] Information provided by Chiesi Limited – not confidential.

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