NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Evinacumab for treating homozygous familial hypercholesterolemia in children

Company/Developer	Ultragenyx

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29286	NICE ID: 11806	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

Evinacumab is currently in clinical development for the treatment of homozygous familial hypercholesterolaemia (HoFH) in children aged 5-11 years. HoFH is a rare genetic disease that occurs when two of the familial hypercholesterolaemia (FH) causing genes are inherited, one from each parent, resulting in dangerously high levels of 'bad' cholesterol (low-density lipoprotein-cholesterol [LDL-C]). This increases the risk of developing heart disease and life-threatening cardiac events as early as teen years. Without treatment, serious cardiovascular complications can occur. Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and machines that remove cholesterol from the blood. Despite these therapies, most patients with this disorder do not reach guideline-recommended LDL cholesterol levels.

Evinacumab is human monoclonal antibody (a type of protein) which binds to and inhibits a protein called angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 can slow down or block enzymes that break down fats. Once Evinacumab attaches to ANGPTL3, it stops the protein from blocking these enzymes, which lowers the levels of fats and reduces cholesterol. Therefore, evinacumab leads to a significant decrease in circulating fats in patients. Evinacumab will be administered as an intravenous dose. If approved, evinacumab will provide an alternative treatment option for paediatric HoFH.

Proposed Indication

Treatment of paediatric patients aged 5 to 11 years with homozygous familial hypercholesterolemia (HoFH), alongside their lipid-lowering treatment regimen.[1,2]

Technology

Description

Evinacumab (Evkeeza, REGN1500) is a human monoclonal antibody which binds and inhibits angiopoietin-like protein 3 (ANGPTL3).[1,2] The inhibition of ANGPTL3 leads to increased activity of the lipoprotein lipase (LPL) and the endothelial lipase (EL). LPL is the main enzyme for hydrolyzation of triglyceride-rich lipoproteins. EL is a phospholipase which preferentially hydrolyzes high-density lipoprotein (HDL) but also decreases circulating low-density lipoprotein-cholesterol (LDL-C). The increased LPL and EL activity reduces circulating levels of very-low-density lipoprotein cholesterol, triglycerides, LDL-C and HDL-cholesterol. Evinacumab leads to a significant decrease in circulating lipids and attainment of lipid targets in these patients.[2]

Evinacumab is in clinical development for the treatment of HoFH in paediatric patients.[1] In the phase III trial (NCT04233918). evinacumab will be administered as a single intravenous (IV) dose of 15mg/kg once every 4 weeks (Q4W) until week 20.[1,3]

Key Innovation

HoFH is characterised by a markedly elevated plasma LDL-C level from birth, which results in an increased risk of premature atherosclerotic cardiovascular disease (CVD). Attempts to lower cholesterol 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 cholesterol levels.[4] In a separate phase III trial, patients aged 12 years and older with HoFH receiving maximum doses of lipid-lowering therapy, the reduction from baseline in the LDL-C level in the evinacumab group, as compared with the small increase in the placebo group, resulted in a between-group difference of 49.0 percentage points at 24 weeks, showing evinacumab substantially lowered LDL cholesterol levels.[4]

Evinacumab is the first ANGPTL3-targeted therapy approved by the FDA (as evinacumab-dgnb) and European Commission as an adjunct therapy for certain patients aged 12 years and older with HoFH.[3] If approved, it would provide an alternative treatment option for paediatric patients aged 5 to 11 years also with HoFH.

Regulatory & Development Status

Evinacumab is currently licensed in the EU for the treatment of adults and adolescents aged 12 years and older with HoFH.[5]

Evinacumab is also currently in phase II/III clinical trials for the treatment of hypercholesterolemia and hypertriglyceridemia.[6]

Evinacumab has the following regulatory designations/awards:[7,8]

- An Orphan Drug in the USA in 2016 for the treatment HoFH.
- A Breakthrough Therapy by the US FDA for HoFH in April 2017.

Patient Group

Disease Area and Clinical Need

Homozygous familial hypercholesteraemia (HoFH) is a form of FH (familial hypercholesterolaemia). This is a condition which is passed down through families in the genes and raises the blood cholesterol to very high levels. HoFH is the more severe form and it raises the cholesterol even higher.[9] HoFH occurs when two copies of the FH-causing genes are inherited, one from each parent, resulting in dangerously high levels (>400 mg/dL) of LDL-C, or bad cholesterol. Those living with HoFH are at risk for premature atherosclerotic disease and life-threatening cardiac events as early as their teen years.[3] Without treatment, HoFH can lead to heart disease at a very young age, even in childhood. HoFH raises the cholesterol from the time a person is born and symptoms often appear in childhood.[9] Patients usually have xanthomas (skin lesions) by early childhood. Planar xanthomas affecting the skin on the hands, elbows, buttocks and knees in a young child are diagnostic for this condition. Corneal arcus surrounding the entire inside edge of the cornea is often present. Most individuals with HoFH experience severe coronary artery disease (CAD) 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. Very aggressive therapy is needed to reduce the likelihood of vascular events.[10]

Familial hypercholesteremia (FH) in the UK population is believed to be approximately 1 in 250, meaning about 220,000 people in the UK have FH, of whom less than 8% are currently identified.[11] It is estimated that up to 56,000 children in the UK may have FH but only 600 of these are known.[12] In England (2020-21), there were 1,551 finished consultant episodes (FCEs) and 1,371 admissions for a primary diagnosis of pure hypercholesterolaemia (ICD-10 code E78.0), which resulted in 895 day cases and 3,408 FCE bed days for all ages. There were 109 patients aged 5-14 years with a primary diagnosis of pure hypercholesterolaemia.[13] HoFH is considered a rare disease in the UK, with approximately 80 cases of HoFH in the UK compared with up to 8,000 cases of other rare diseases, as reported by HEART UK in 2016.[14] The estimated prevalence of HoFH is estimated to 1 per 1 million population in the UK, although this may be an underestimate because of phenotypic variation.[14,15] 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.[15]

Recommended Treatment Options

Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. For children and young people with FH, a statin that is licensed for use in the appropriate age group may be used. In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering: a higher dose of statin than is licensed for use in the appropriate age group, and/or more than one lipid-modifying drug therapy, and/or lipid-modifying drug therapy before the age of 10 years.[16]

In children and young people with HoFH, LDL-C concentration may be lowered by lipid-modifying drug therapy and this should be considered before LDL apheresis (a treatment that removes cholesterol from the blood). In children and young people with FH who are intolerant of statins, healthcare professionals should consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration (such as bile acid sequestrants [resins], fibrates or ezetimibe).[16]

Clinical Trial Information

Trial	NCT04233918; EudraCT- 2019-001931-30; A Three-Part, Single-Arm, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Evinacumab in Pediatric Patients With Homozygous Familial Hypercholesterolemia **Phase III –** Active, not recruiting **Location(s) –** 2 countries in EU, US, Australia, Taiwan and Ukraine **Study completion date –** January 2022
Trial Design	Single group assignment, open label
Population	N = 20 (actual); diagnosis of functional HoFH by either genetic or clinical criteria as defined in the protocol; 5 to 11 years
Intervention(s)	Evinacumab single IV dose Q4W
Comparator(s)	No comparator
Outcome(s)	**Primary outcomes:** • PK parameter: Maximum serum concentration observed (Cmax) [Time frame: up to week 24] • PK parameter: Area under the concentration-time curve (AUC) [Time frame: up to week 24] • PK parameter: Observed terminal half-life linear (t1/2) [Time frame: up to week 24] • Percent change in calculated low-density lipoprotein cholesterol (LDL-C) from baseline to week 24 [Time frame: week 24] See trial record for full list of other outcomes.
Results (efficacy)	Despite treatment with other lipid-lowering therapies, children (n=14) entered the trial with an average LDL-C level of 264 mg/dL, more than twice the target (<130 mg/dL) for paediatric patients with HoFH. After 24 weeks of evinacumab treatment (15 mg/kg every 4 weeks delivered IV), the Phase 3 trial met its primary endpoint with additional results showing:[3] • 79% of patients reduced their LDL-C by at least half • An absolute 132 mg/dL reduction in LDL-C from baseline, on average • Reductions in levels of all lipid endpoint parameters assessed, which were generally observed within the first 8 weeks of treatment. These lipid parameters were apolipoprotein B, non-high-density lipoprotein cholesterol, lipoprotein(a) and total cholesterol.
Results (safety)	Evinacumab was generally well-tolerated with all patients completing the trial. The most common adverse events (AEs) were throat pain (oropharyngeal pain, 21%) as well as upper abdominal pain, diarrhoea, headache and nasopharyngitis (all 14%). There were two severe AEs (aortic stenosis and tonsilitis), both of which were considered unrelated to treatment.[3]

Estimated Cost

The cost of evinacumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). September 2016.
- 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. 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

- Lui DTW, Lee ACH, Tan KCB. Management of Familial Hypercholesterolemia: Current Status and Future Perspectives. January 2021.[17]
- McGowan MP, Dehkordi SHH, Moriarty PM, and Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. December 2019.[18]
- Japan Paediatric Society and Japan Atherosclerosis Society for Making Guidance of Paediatric Familial Hypercholesterolemia (FH). Guidance for Paediatric Familial Hypercholesterolemia 2017. June 2018.[19]

Additional Information

Regeneron Pharmaceuticals, Inc. and Ultragenyx Pharmaceutical Inc. announced in January 2022 a license and collaboration agreement for Ultragenyx to clinically develop, commercialize and distribute evinacumab in countries outside of the U.S.[20]

Ultragenyx 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

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