

HEALTH TECHNOLOGY BRIEFING

AUGUST 2019

Evinacumab for homozygous familial hypercholesterolemia

NIHRIO ID	10932	NICE ID	10057
Developer/Company	Regeneron Pharmaceuticals Inc.	UKPS ID	

Licensing and market availability plans	Currently in phase III clinical trial
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SUMMARY

Evinacumab is in clinical development for the treatment of homozygous familial hypercholesterolemia (HoFH). Familial hypercholesterolemia (FH) is an inherited condition where a person's cholesterol levels are higher than normal from birth as the liver is unable to break down or remove excess cholesterol. Specifically, FH patients have severe elevations in low density lipoprotein cholesterol (LDL-C) levels. This can lead to heart disease at a relatively young age. HoFH is a very rare and severe form of the disease which results from inheriting a faulty gene from both parents resulting in little or no LDL receptor activity. Treatment of hypercholesterolemia in patients with HoFH can be challenging with the current therapies and there is need for new treatments.

Evinacumab is a monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 is produced in the liver and regulates levels of triglycerides, LDL-C, and high-density lipoprotein cholesterol, in the blood. Evinacumab binds to and inhibits ANGPTL3 and lowers cholesterol thereby having the potential to reduce cardiovascular risk. Results from early studies have shown that evinacumab has the potential to result in clinically significant LDL-C reductions in HoFH patients.

PROPOSED INDICATION

Homozygous familial hypercholesterolemia aged 12 years and older.^{1,2}

TECHNOLOGY

DESCRIPTION

Evinacumab (REGN1500) is a fully human monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3). Evinacumab binds with high affinity to ANGPTL3 which plays a central role in lipoprotein metabolism.³ ANGPTL3 is a liver-derived protein that regulates lipid metabolism, primarily through inhibiting lipoprotein lipase (LPL) and endothelial lipase. Previous genetic studies suggested that loss-of-function (LOF) mutations in the ANGPTL3 gene were associated with lower levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum triacylglycerols (TGs) compared to non-carriers.⁴⁻⁷ Preclinical studies and human genetic analyses suggest that inhibition of ANGPTL3 lowers levels of LDL cholesterol and could reduce the risk of cardiovascular events.⁸ In a large human genetics study evaluating the relationship between ANGPTL3 LOF variants and coronary artery disease, individuals heterozygous for ANGPTL3 LOFs had lower ANGPTL3 levels and lower odds of coronary artery disease than non-carriers. These findings suggest a cardiovascular risk benefit associated with genetic “antagonism” of ANGPTL3 (via decreased LDL-C and TGs).⁹

Evinacumab is in clinical development for homozygous familial hypercholesterolemia (HoFH). In the phase III clinical trial (NCT03399786/EudraCT: 2017-001388-19) evinacumab 15 mg/kg or placebo is administered via intravenous injection (IV) every 4 weeks for 24 weeks, then evinacumab 15 mg/kg IV for 24 weeks.^{2,10} In the phase III long-term safety and efficacy clinical trial (NCT03409744/EudraCT: 2017-003170-13), evinacumab 15 mg/kg IV is administered for up to 4 years.^{1,11}

INNOVATION AND/OR ADVANTAGES

HoFH is a rare and serious condition that is frequently caused by mutations in both alleles of the LDL receptor (LDLR) gene and results in the decreased clearance of LDL particles from plasma. Treatment of hypercholesterolemia in patients with HoFH is challenging because the current existing treatment options have either a diminished response as compared to non-HoFH patients and/or issues with tolerability. While statins and PCSK9 inhibitors can reduce LDL-C by more than 50% in non-familial hypercholesterolemic patients, patients with HoFH tend to be refractory to these therapies because the mechanism of action generally lowers LDL-C levels through up-regulation of LDLR and these patients have near total loss of functional LDLRs.¹²⁻¹⁵

Other drugs for HoFH, mipomersen and lomitapide, can provide additional LDL-C reductions, but are associated with tolerability issues as well as safety concerns.^{15,16} Because of these limitations of drug treatment, the majority of patients with HoFH are candidates for lipoprotein apheresis,¹⁷ which is costly, burdensome on patients and has limited availability.

Therefore, there exists an unmet medical need to reduce LDL-C and the inevitable risk for premature cardiovascular diseases in patients with HoFH, especially those with null/null mutations for LDLR for which most therapies show little or no benefit. Results from a proof-of-concept study have shown that evinacumab is likely to result in clinically significant LDL-C reductions in HoFH patients, including in patients that have two LDLR negative alleles.¹⁸

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Evinacumab has the following regulatory designations/ awards:

- An orphan drug in the USA in 2016 for the treatment of homozygous familial hypercholesterolemia.¹⁹
- A Breakthrough Therapy by the FDA for the treatment of homozygous familial hypercholesterolemia in March 2017.²⁰

PATIENT GROUP

DISEASE BACKGROUND

Familial hypercholesterolaemia (FH) is an inherited disorder where the liver is incapable of metabolising or removing excess low density lipoprotein (LDL) cholesterol.²¹ The most common FH cause is mutations along the entire gene that encode for LDL receptor (LDLR) protein, but it has been also described that mutations in apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes produce this phenotype.²² This can lead to very high LDL levels which increase the risk of premature cardiovascular disease. It is estimated that over 90% of people with FH have not been properly diagnosed.²¹ There are two forms of FH; heterozygous and homozygous. Homozygous FH (HoFH) is much less common than heterozygous FH and is more severe. In HoFH, the affected individual inherits gene mutations affecting LDL from both parents (so the individual has two genetic mutations).²³

The classic signs of HoFH are lumps and bumps around the knuckles or Achilles tendon (caused by cholesterol deposits), yellow cholesterol build-up around the eyes and eyelids, or a pale ring around the iris of the eye.²⁴ If undiagnosed and untreated, HoFH can lead to serious cardiac complications, such as premature atherosclerotic cardiovascular disease.²⁵

The results of a systematic review and meta-analysis published in 2018 indicate that FH does not impact negatively on symptoms of anxiety and depression, and on health-related quality of life.²⁶ However, evidence from individual studies indicates that the impact of FH on quality of life may vary according to specific factors, including treatment efficacy,²⁷ presence of cardiovascular disease, patient age and gender.²⁸

CLINICAL NEED AND BURDEN OF DISEASE

Homozygous FH is rare, presents in children and is associated with early death from cardiovascular disease. HoFH has an incidence of approximately one case per million.²⁹ According to the 2018 mid-year population estimates,³⁰ this would equate to 56 people with HoFH in England.

The Hospital Episodes Statistics for England 2017/2018 recorded 558 finished consultant episodes, 535 hospital admissions, 243 bed days and 422 day cases due to pure (familial) hypercholesterolaemia (ICD 10 code E78).³¹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The management of familial hypercholesterolaemia involves the provision of lifestyle advice and drug treatments. Lifestyle advice should be offered in relation to alcohol consumption, smoking, weight management, diet and physical activity.³²

In patients with HoFH younger than 16 years of age, LDL cholesterol (LDL-C) concentration may be modestly lowered by lipid-modifying drug therapy and this should be considered before LDL apheresis. Prescribing of drug therapy for people aged 16 and over with HoFH should be undertaken within a specialist centre.³²

In children or young persons with FH who are aged under 16 years, lipid-modifying drug therapy should usually be considered by the age of 10 years. The decision to defer or offer lipid-modifying drug therapy for a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors, including their LDL-C concentration. For individuals with FH who are aged 16 years and over, healthcare professionals should offer referral to a specialist with expertise in FH for consideration for further treatment if the affected individual is assessed to be at very high risk of a coronary event, that is, if they have any of the following: established coronary heart disease, a family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative) or two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes).

In women of child bearing age, the risks for future pregnancy and the fetus while taking lipid-modifying drug therapy should be discussed. This discussion should be revisited at least annually.

Liver transplant is considered as an option for the treatment of people with HoFH after treatment with lipid-modifying drug therapy and LDL apheresis.³²

CURRENT TREATMENT OPTIONS

Statins are first-line therapy for treating familial hypercholesterolaemia:³³

- When offering lipid-modifying drug therapy to adults with FH, healthcare professionals should inform the person that this treatment should be lifelong.
- Offer a high-intensity statin with the lowest acquisition cost as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL-C concentration from the baseline measurement
- The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment)

Evolocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:³²

- The dosage is 140 mg every 2 weeks.
- Low-density lipoprotein concentrations are persistently above the thresholds specified in low-density lipoprotein cholesterol concentrations above which evolocumab is recommended despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by (the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).

- The company provides evolocumab with the discount agreed in the patient access scheme.

Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:³²

- Low-density lipoprotein concentrations are persistently above the thresholds specified in low-density lipoprotein cholesterol concentrations above which alirocumab is recommended despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).
- The company provides alirocumab with the discount agreed in the patient access scheme.

PLACE OF TECHNOLOGY

If licensed, evinacumab will offer an additional treatment option for individuals with homozygous familial hypercholesterolemia, a condition for which there are limited available therapies.

CLINICAL TRIAL INFORMATION

Trial	NCT03399786, Eudra CT 2017-001388-19; aged 12 years and older; evinacumab vs placebo; phase III
Sponsor	Regeneron Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry ^{2,34}
Location	Seven EU countries (not incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled
Participants	N=57 (estimated); aged 12 years and older; diagnosis of functional HoFH; if undergoing LDL apheresis, must have initiated LDL apheresis at least 3 months prior to screening and must have been on a stable weekly or every other week schedule and/or stable settings for at least 8 weeks; willing to consistently maintain his/her usual low fat or heart-healthy diet for the duration of the study
Schedule	Randomised to IV administration of 15 mg/kg IV evinacumab every 4 weeks; IV administration of placebo
Follow-up	24 weeks
Primary Outcomes	Percent change in calculated LDL-C from baseline to week 24
Secondary Outcomes	<p><u>Week 24 for all outcomes listed below</u></p> <ul style="list-style-type: none"> • Percent change in Apolipoprotein B (Apo B) from baseline • Percent change in non-High-density lipoprotein cholesterol (HDL-C) from baseline • Percent change in Total cholesterol (TC) from baseline • Proportion of patients with ≥30% reduction in calculated LDL-C

	<ul style="list-style-type: none"> • Proportion of patients with $\geq 50\%$ reduction in calculated LDL-C • Proportion of patients with LDL-C < 100 mg/dL [2.59 mmol/L] • Change in calculated LDL-C from baseline to week 24 • Proportion of patients who meet European Union (EU) apheresis eligibility criteria (see German Apheresis Working Group) • Proportion of patients who meet United States (US) apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria) • Percent change in Triglyceride (TG) from baseline • Change in Apo B from baseline • Change in non-HDL-C from baseline • Change in TC from baseline • Percent change in lipoprotein a [Lp(a)] from baseline • Proportion of patients with LDL-C < 70 mg/dL [1.81 mmol/L] • Percent change in apolipoprotein CIII (Apo CIII) from baseline • Total evinacumab concentration in serum Incidence of anti-drug antibody (ADA)
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as April, 2019

Trial	NCT03409744 , EudraCT 2017-003170-13; aged 12 years and older; evinacumab; phase III
Sponsor	Regeneron Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry ^{1,35}
Location	Eight EU countries (incl UK), Canada, United States and Ukraine
Design	Non-randomised, uncontrolled, single group assignment, open label
Participants	n=100 (estimated); patients with homozygous familial hypercholesterolemia; aged 12 years and older; completion of the parent study in which they participated; able to understand and complete study-related questionnaires
Schedule	Assigned to receive evinacumab via intravenous administration
Treatment Duration	192 weeks
Primary Outcomes	Incidence and severity of treatment-emergent adverse events
Secondary Outcomes	<ul style="list-style-type: none"> • Percent change in low-density lipoprotein cholesterol (LDL-C) over time • Absolute change in LDL-C over time • Percent change in Apolipoprotein B (Apo B) over time • Absolute change in Apo B over time

	<ul style="list-style-type: none"> • Percent change in non-High-Density Lipoprotein Cholesterol (HDL-C) over time • Absolute change in non-HDL-C over time • Percent change in total cholesterol (TC) over time • Absolute change in TC over time • Percent change in triglycerides (TGs) over time • Absolute change in TGs over time presence of anti-evincumab antibodies
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as April 11, 2022

ESTIMATED COST

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RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA394). June 2016.
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- NICE technology appraisal guidance. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolemia (TA385). February 2016.
- NICE clinical guideline. Familial hypercholesterolemia: identification and management (CG71). November 2017.
- NICE quality standard. Familial hypercholesterolemia (QS41). August 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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