Innovation Observatory

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Bempedoic acid for primary hypercholesterolaemia or mixed dyslipidaemia in patients unable to reach cholesterol goals with the maximum tolerated dose of a statin

NIHRIO ID	6055	**NICE ID**	9970
Developer/Company	Esperion Therapeutics Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Bempedoic acid is an oral medicinal product that is in clinical development for the treatment of people with primary hypercholesterolaemia or mixed dyslipidaemia with high cardiovascular risk. Abnormal levels of lipids in the blood characterises dyslipidaemia. High levels of cholesterol in the blood (hypercholesterolemia) may be caused by genetic defects as seen in familial hypercholesterolaemia, or may occur when genes and other factors such as lifestyle habits interact, as seen in non-familial hypercholesterolaemia. Most people with hypercholesterolaemia have mildly or moderately increased low-density lipoprotein cholesterol (LDL-C) levels (often considered the "bad" cholesterol that may cause blockages of blood vessels). Elevated levels of LDL-C increases the risk of cardiovascular disease, which is responsible for many deaths and disabilities.

Bempedoic acid lowers LDL-C via a different mechanism of action and offers the potential advantage of reduced muscular adverse effects when compared to statins which are the current standard of care. Bempedoic acid is being developed for patients at high cardiovascular risk who are unable to reach LDL-C goals with the maximum tolerated dose of statins. The effect of bempedoic acid is additive—not redundant—to that of statins, and if licensed, may offer additional and effective treatment option to use in combination with dietary changes and other lipid-modifying therapies to treat primary hypercholesterolaemia or mixed dyslipidaemia.

PROPOSED INDICATION

Primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in patients with high cardiovascular risk and unable to reach low density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a statin - adjunct to diet in combination with a statin or statin with other lipid lowering therapies.[a]

TECHNOLOGY

DESCRIPTION

Bempedoic acid (ETC-1002), a small molecule drug, promotes low density lipoprotein (LDL) receptor-mediated clearance of LDL-cholesterol (LDL-C) by inhibition of adenosine triphosphate citrate lyase (ACL), a mechanism complementary to those of existing lipid-modifying therapies. Bempedoic acid is a pro-drug activated specifically within the liver where it inhibits ACL, a regulatory checkpoint within the cholesterol biosynthesis pathway. By inhibiting ACL, bempedoic acid reduces cholesterol synthesis in liver cells and triggers compensatory LDL receptor upregulation. Inhibiting ACL with bempedoic acid complements other mechanisms targeted by current therapies, resulting in additional lowering of LDL-C, without leading to increases in adverse events (AEs).[b]

In the phase III clinical trials (NCT02666664, NCT02991118) of patients with high cardiovascular risk and elevated LDL-C not adequately controlled by their current therapy, patients are given a daily dose of 180 mg bempedoic acid as an oral tablet, whilst remaining on ongoing lipid-modifying therapy.[1,2]

INNOVATION AND/OR ADVANTAGES

The current standard of care for patients with hypercholesterolaemia is primarily statins which are capable of reducing LDL-C. However, some patients, particularly those with heterozygous familial hypercholesterolaemia, coronary heart disease (CHD), CHD-risk equivalents, and other clinical manifestations of atherosclerotic cardiovascular disease (ASCVD), require additional LDL cholesterol lowering on top of what can be achieved with maximum tolerated statin therapy. Additionally there are patients who are unable to tolerate statins due to adverse advents such as muscle pain, or increased blood glucose. There is an unmet medical need for patients unable to achieve sufficient reduction in LDL cholesterol with existing treatment options and thus remain at increased risk of cardiovascular disease and the consequences thereof.[3]

Bempedoic acid requires activation by a specific enzyme acyl-CoA synthatase (ACSVL1), which is largely restricted to the liver. Therefore, it is believed that unlike statins, myotoxicity is unlikely to occur with bempedoic acid because it does not inhibit cholesterol biosynthesis in skeletal muscle due to the absence of ACSVL1 in these cells. The effect of bempedoic acid is additive—not redundant—to that of statins, because the target of bempedoic acid, ACL, is a distinct regulatory checkpoint on the cholesterol biosynthesis pathway than HMG-CoA reductase, the primary target of statins.[b]

[a] Company provided the full indication
[b] Company information

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bempedoic acid does not currently have Marketing Authorisation in the EU/UK for any indication.[4]

- Bempedoic acid or bempedoic acid with ezetimibe in a fixed-dose combination are in phase III clinical trials for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in patients who are statin-intolerant, or for whom a statin is contraindicated.[5, 6]

- Bempedoic acid monotherapy and bempedoic acid with ezetimibe in a fixed-dose combination is also in phase III clinical trials for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in patients unable to reach LDL- Cholesterol goals with the maximum tolerated dose as an adjunct to diet in combination with a statin or statin with other lipid lowering therapies.[7]

PATIENT GROUP

DISEASE BACKGROUND

Dyslipidaemia is a broad term describing a number of conditions, including hypercholesterolaemia, hyperlipidaemia and mixed dyslipidaemia, in which disturbances in lipid metabolism lead to changes in the concentrations of lipids in the blood. Mixed dyslipidaemia is defined as elevations in LDL-C cholesteroand triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol.[8] Along with other cardiovascular risk factors, dyslipidaemia may lead to the development of atherosclerosis and cardiovascular disease (CVD).[9] Dyslipidaemia, and more specifically elevated LDL cholesterol, is known to be a causal factor of ASCVD. Epidemiological studies indicate a strong relationship between elevated LDL-C with the development of CVD.[10, 11] The reduction in cardiovascular events with pharmacological therapy aimed at LDL lowering is well documented in both primary prevention and secondary prevention.[12] A meta-analysis of 26 trials of >170,000 randomised patients demonstrated a reduction in major CV events of about 22% per each mmol/L reduction in LDL-C.[13]

Hypercholesterolaemia is characterised by high cholesterol concentration in the blood, specifically elevated LDL-C. This may be caused by a single genetic defect, as seen in familial hypercholesterolaemia (FH), or may arise following the interaction of multiple genes with dietary and other risk factors, such as smoking and physical inactivity, seen in non-familial hypercholesterolaemia.[14] The majority of people with primary hypercholesterolaemia have mildly or moderately elevated cholesterol levels and exhibit few clinical symptoms yet they can still be at elevated risk for premature CVD. Severe hypercholesterolaemia can cause xanthomas and arcus corneae. However, the increased risk of CVD is the most significant problem associated with hypercholesterolaemia, as atherosclerosis can cause angina, myocardial infarction and stroke.[14, 15]

Total cholesterol (TC) and LDL-C levels constitute the primary targets of therapy as there is compelling evidence to indicate that reducing TC and LDL-C can prevent CVD,[16] however, the use of statins to control this is not possible in some patients as they require greater reductions in LDL-C that they can get from a statin or they cannot tolerate the dose due to the associated side effects.[17] Statin intolerance can range from “complete intolerance” of any statin at any dose to the inability to tolerate statins that provide an optimal reduction in LDL-C and has also been associated with increased risk for non-fatal CV events and lower likelihood of achieving optimal LDL-C goals.[18]

CLINICAL NEED AND BURDEN OF DISEASE

Primary non-familial hypercholesterolaemia affects around 4% of the adult population of England (an estimated 2.2 million people using the 2017 mid-year population estimates)[19] of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment. Primary heterozygous FH is less common (1 in 500) and affects about 106,000 people in England, although only an estimated 15-17% are diagnosed.[14]

People with hypercholesterolaemia have an increased risk of CVD. In 2016-17, the prevalence of CVD was approximately 5.9 million in the England.[20] CVD is associated with the majority of mortality in England and is the leading cause of death in England and Wales.[21] In 2016, there were 56.7 deaths per 100,000 registered in England, for CVD in those aged 0-74 years, which equates to 28,949 deaths.[22] I In addition to the increased mortality associated with chronically elevated LDL-C, the disease burden and morbidity associated with CVD are significant, resulting in substantial economic burden for the UK.[23]

The incidence of statin intolerance is estimated at 5-10% due to non-severe side effects, the majority of which are muscle-related. [24] In a large observational study conducted in France, statin discontinuation was reported in 20% of hyperlipidaemic patients due to adverse muscular symptoms.[25]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Managing hypercholesterolaemia involves dietary and lifestyle changes (such as smoking cessation, weight loss and increased physical activity), and treatment with a lipid-regulating drug if appropriate. Starting drug treatment is generally based on an assessment of the person's CVD risk.[14]

CURRENT TREATMENT OPTIONS

Current lipid modification therapy options for hypercholesterolaemia include:

- High-intensity statin with the lowest acquisition cost is recommended as the initial treatment for all adults with FH for the 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).[26]
- Ezetimibe as a monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated, or who cannot tolerate statin therapy.[27] Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when serum total or LDL cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and when a change from initial statin therapy to an alternative statin is being considered.[27,28]
- Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration.[26]
- Evolocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, if the dosage is 140 mg every 2 weeks and LDL concentrations are persistently above

the thresholds specified in NICE technology appraisal guidance [TA394] 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).[30,29]

- Evolocumab and alirocumab are recommended by NICE as options for treating primary hypercholesterolaemia or mixed dyslipidaemia if LDL-C is ≥3.5mmol/L in patients at very high risk of CVD, and ≥4.0mmol/L in patients at risk of CVD.[30]
- Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, if LDL concentrations are persistently above the thresholds specified in NICE technology appraisal guidance [TA393] 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).[29,31]

PLACE OF TECHNOLOGY

Bempedoic acid may offer an additional treatment option for patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who are unable to reach LDL-C goals with the maximum tolerated dose of a statin or statin with other lipid lowering therapies.

CLINICAL TRIAL INFORMATION

Trial	**CLEAR Harmony, NCT02666664, 1002-040, EudraCT 2015-004136-36; bempedoic acid vs placebo; phase III**	**CLEAR Harmony OLE, NCT03067441, 1002-050, EudraCT 2016-004115-12; bempedoic acid; phase III extension**
Sponsor	Esperion Therapeutics	Esperion Therapeutics
Status	Completed	Ongoing
Source of Information	Trial registry,[1] press release[32,33]	Trial registry[34]
Location	EU (incl UK), USA, Canada.	USA
Design	Randomised, placebo-controlled, parallel assignment, double-blind	Single group assignment, open-label extension
Participants	n= 2230; aged 18 years and older; hyperlipidaemia (fasting LDL-C ≥ 70 mg/dL); high cardiovascular risk; on maximally tolerated lipid-modifying therapy	n=1452; aged 18 years and older; successfully completed CLEAR Harmony (1002-040) parent study
Schedule	Randomised to bempedoic acid 180 mg tablets taken orally, once per day or matching placebo tablets taken orally, once per day. Patients remain on ongoing statin therapy.	Bempedoic acid 180 mg tablets taken orally, once per day.
Follow-up	Active treatment period not reported Follow-up: 52 weeks	Active treatment period not reported Follow-up: 78 weeks

Primary Outcomes	Number of participants with treatment-related adverse events as assessed by MedDRA 18.1 [Time Frame: Baseline through 52 weeks]	Number of participants with treatment-related adverse events as assessed by MedDRA 18.1 [Time Frame: Baseline through 78 weeks]
Secondary Outcomes	Time Frame: 12, 24, and 52 weeks • Percent change in LDL-C • Percent change in high-sensitivity C-reactive protein (hs-CRP) Other Outcome Measures: Time Frame: 12, 24, and 52 weeks • Percent change in non-HDL-C • Percent change in TC • Percent change in apolipoprotein B (apoB)	Time Frame: Baseline to Weeks 52 and 78 • Percent change in LDL-C • Change in LDL-C • Percent change in TC • Percent change (ApoB) • Percent change in hs-CRP • Percent change in Trigycerides • Percent change in HDL-C
Key Results	The study met the primary endpoint of safety and tolerability and the key efficacy endpoint: • There were no clinically relevant differences between the bempedoic acid and placebo groups in the occurrence of AEs with 78.5 percent and 78.7 percent, respectively; or serious adverse events (SAEs) with 14.5 percent and 14.0 percent, respectively. Discontinuations due to AEs were 10.9 percent and 7.1 percent, respectively for the bempedoic acid and placebo groups; discontinuations due to muscle-related AEs were 2.2 percent and 1.9 percent, respectively in the bempedoic acid and placebo groups. In the study, 0.54 percent of patients treated with bempedoic acid and 0.13 percent of patients in the placebo group had elevations in liver function tests (ALT/AST) of greater than three times the upper limit of normal, repeated and confirmed. The cumulative number of patients now treated with bempedoic acid in phase 2 and phase 3 clinical trials totals 2,434. Of these, 0.58 percent had elevations in liver function tests greater than three times the upper limit of normal, repeated and confirmed. This rate of elevations in liver function test is consistent with the rate observed in all other previously approved oral LDL-C-	-

	lowering therapies, including statins and ezetimibe. • On-treatment LDL-C achieved a lowering of 20 percent at 12 and 24 weeks, and 16 percent at 52 weeks (p<0.001). The LDL-C lowering for the bempedoic acid group at 12 weeks was 18 percent from baseline, as compared to an LDL-C increase of two percent for the placebo group. The intent to treat LDL-C lowering totaled 18 percent (p<0.001) at 12 weeks. These results were comparable across statin treatment groups. Patients treated with bempedoic acid also achieved a significant reduction of 22 percent in hsCRP, compared to the placebo group which had an increase of three percent (p<0.001).	
Adverse effects (AEs)	Patients on bempedoic acid who were on a maximally tolerated statin dose had significantly fewer instances of new-onset or worsening diabetes than those on placebo who were on a maximally tolerated statin dose (5.4 percent compared to 3.3 percent; p<0.02).	-
Expected reporting date	-	Study completion date reported as December 2019.

Trial	**CLEAR Wisdom, NCT02991118, 1002-047, EudraCT 2016-003486-26; bempedoic acid vs placebo, phase III.**
Sponsor	Esperion Therapeutics
Status	Ongoing
Source of Information	Trial registry[2]
Location	USA
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n= 779; aged 18 years and older; hyperlipidaemia (fasting LDL-C ≥ 70 mg/dL); high cardiovascular risk; on maximally tolerated lipid-modifying therapy.
Schedule	Randomised to bempedoic acid 180 mg tablets taken orally, once per day or matching placebo tablets taken orally, once per day. Patients remain on ongoing lipid-modifying therapy.
Follow-up	Active treatment period not reported Follow-up: 12 weeks

Primary Outcomes	Percent change in LDL-C [Time Frame: Baseline through 12 weeks]
Secondary Outcomes	None reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as September 2018.

ESTIMATED COST

The price of bempedoic acid is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393). June 2016
- NICE technology appraisal. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA394). June 2016
- NICE technology appraisal. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). February 2016
- NICE clinical guideline. Familial hypercholesterolaemia: identification and management (CG71). November 2017
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). July 2016
- NICE quality standard. Cardiovascular risk assessment and lipid modification (QS100). September 2015

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- European Society of Cardiology/European Atherosclerosis Society. European guidelines on cardiovascular disease prevention in clinical practice. 2016[35]
- American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. 2013[36]
  European Society of Cardiology and European Atherosclerosis Society. Guidelines on management of dyslipidaemia. 2011[9]

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