Innovation Observatory

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Bempedoic acid (monotherapy) or bempedoic acid in combination with ezetimibe for primary hypercholesterolaemia or mixed dyslipidaemia

NIHRIO ID	12682	**NICE ID**	9973
Developer/Company	Esperion Therapeutics Inc	**UKPS ID**	N/A

Licencing and market availability plans	Bempedoic acid (monotherapy) or bempedoic acid in combination with ezetimibe is currently in phase III trials

SUMMARY

Bempedoic acid as a monotherapy, or in combination with ezetimibe, is in clinical development for high risk and very high risk people with primary hypercholesterolaemia or mixed dyslipidaemia. Abnormal levels of lipids in the blood characterises dyslipidaemia. High levels of cholesterol in the blood (hypercholesterolemia) may be caused by inherited 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. Elevated levels of LDL-C increase the risk of cardiovascular disease, which is responsible for many deaths and disabilities.

The current standard of care for patients with hypercholesterolaemia is primarily statins which are capable of reducing LDL-C. There is however a subset of patients who are unable to tolerate statins due to adverse effects. Bempedoic acid monotherapy or in combination with ezetimibe are once-daily tablets in development for patients unable to tolerate statins at all, or are not able to tolerate the necessary dose of statin required to reach their LDL-C goal, or are recommended not to use them due to various circumstances. Bempedoic acid and ezetimibe both act in complementary ways to lower LDL-C. These therapies may offer additional and effective treatment options 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 who are statin-intolerant, or for whom a statin is contraindicated – adjunct to diet alone or in combination with other lipid-lowering therapies[a]

TECHNOLOGY

DESCRIPTION

Bempedoic acid, 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 triggers compensatory LDL receptor upregulation in response to suppression of cholesterol synthesis in the liver. 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). Bempedoic acid is only active in cell types that express 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. The effect of bempedoic acid is additive—not redundant—to that of statins, because the target of bempedoic acid, ACL, is a different enzyme on the cholesterol biosynthesis pathway than HMG-CoA reductase, the primary target of statins.[b]

Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related dietary sterols. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-lowering therapies. The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.[1]

Bempedoic acid or bempedoic acid in combination with ezetimibe are in phase III development for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in patients who are statin-intolerant, or for whom a statin is contraindicated. These products are being developed as an adjunct to diet alone or in combination with other lipid-lowering therapies.[a] In a phase III clinical trial (CLEAR Serenity; NCT02988115), patients are given a daily dose of 180 mg bempedoic acid (monotherapy) as an oral tablet, whilst remaining on ongoing lipid-modifying therapy.[2] In another phase III clinical trial (CLEAR Tranquillity; NCT03001076) patients are given daily bempedoic acid at a dose of 180mg whilst remaining on ongoing ezetimibe at a dose of 10 mg.[3]

INNOVATION AND/OR ADVANTAGES

The current standard of care for patients with hypercholesterolaemia is primarily statins which are capable of reducing LDL cholesterol although some patients still require additional LDL cholesterol

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

lowering on top of what can be achieved with maximum tolerated statin therapy. There is a subset of patients who are unable to tolerate statins who are at risk of the adverse advents such as muscle pain, increased blood glucose, kidney failure and even death. These patients are at high risk for experiencing ASCVD-related events as a result of the underlying disease progression associated with chronically elevated LDL-C. There is an unmet medical need for high risk and very high risk 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.[4]

Clinical evidence suggests that bempedoic acid can elicit a reduction in LDL cholesterol when administered as a monotherapy or combination therapy with ezetimibe, with the most prominent reductions occurring when administered in combination with ezetimibe in patients with a history of statin intolerance.[5] Based on these findings and the complementary mechanisms of action of bempedoic acid and ezetimibe,[b] if licensed, bempedoic acid as a monotherapy or combined with ezetimibe could be an effective treatment option for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in patients who are statin-intolerant, or for whom a statin is contraindicated.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bempedoic acid monotherapy or in combination with ezetimibe does not currently have Marketing Authorisation in the EU/UK for any indication.

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 low-density lipoprotein cholesterol goals with the maximum tolerated dose as an adjunct to diet in combination with a statin or statin with other lipid lowering therapies.[6]

The effects of bempedoic acid on reducing the risk for cardiovascular events is also being studied in a phase III clinical trial.[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 fat metabolism lead to changes in the concentrations of lipids in the blood. Mixed dyslipidaemia is defined as elevations in LDL cholesterol and 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 chronically elevated LDL cholesterol, is known to be a causal factor of ASCVD. Epidemiological studies indicate a strong relationship between elevated LDL-C and reduced levels of high-density lipoprotein cholesterol (HDL-C) with the development of CVD.[10] A meta-analysis of 21 trials of >170 000 randomised patients demonstrated that the incidence of major CV events was reduced by ~25% for each mmol/L reduction in LDL-C.[11] Elevated LDL-C levels are associated with increased vascular inflammation and atherosclerosis.[12,13,14,15]

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,[10] however, the use of statins to control this is not possible in some patients as they cannot tolerate the dose due to muscle-related

side effects.[16] 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.[17]

Hypercholesterolaemia is characterised by high cholesterol concentration in the blood, including elevated LDL-C. This may be caused by a 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.[18] FH can lead to the early development of atherosclerosis and coronary heart disease,[19] and if untreated, an estimated 50% of men and 30% of women with heterozygous FH will develop coronary heart disease by 55 years of age.[20] The majority of people with primary hypercholesterolaemia have mildly or moderately elevated cholesterol levels and exhibit few clinical symptoms. 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.[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 2016 mid-year population estimates)[21] 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.[18] Using mid-year 2016 population estimates for England, this would indicate that primary heterozygous FH affects 88,243 adults people with only 13,236 to 15,001 of these being diagnosed.[22]

People with hypercholesterolaemia have an increased risk of CVD as the long term raised cholesterol levels accelerate the development of atherosclerosis. CVD is associated with the majority of mortality in England and is the leading cause of death in the UK.[23]

In 2016-17, the prevalence of CVD was approximately 5.9 million in the England.[24] 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.[25] In addition to the increased mortality associated with chronically elevated LDL-C, the disease burden and morbidity associated with ASCVD are significant, resulting in substantial economic burden for the UK.[11]

In 2017, there were 72,612,423 prescription items dispensed for lipid-regulating drugs, with a total net ingredient cost of £215,440,981 across England.[26] The incidence of statin intolerance is estimated at 5-10% due to non-severe side effects, the majority of which are muscle-related.[27] In a large observational study conducted in France, statin discontinuation was reported in 20% of hyperlipidaemic patients due to adverse muscular symptoms.[28]

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.[18]

CURRENT TREATMENT OPTIONS

Current lipid modification therapy options for hyperlipidaemia in the primary prevention of CVD include:[23,29]

- 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.
- 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.

Current treatment options for hyperlipidaemia in the secondary prevention of CVD include:[23]

- Fibrates may be considered for secondary prevention in people with CVD who are unable to tolerate statins or in FH in combination with a statin. They are also used in the treatment of severe isolated hypertriglyceridaemia (TG >10mmol/L), but where this coexists with hypercholesterolaemia (i.e. in mixed hyperlipidaemia), LDL-reduction remains the priority and thus statins tend to remain first-line.

If a person is unable to tolerate a high-intensity statin, treat with the maximum tolerated dose.[23]

PLACE OF TECHNOLOGY

Bempedoic acid as a monotherapy or in combination with ezetimibe could be used in a similar line of therapy as NICE TA 385 for treating primary (heterozygous familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated.[30]

CLINICAL TRIAL INFORMATION

Trial	CLEAR Serenity, NCT02988115; bempedoic acid vs placebo; phase III
Sponsor	Esperion Therapeutics
Status	Ongoing
Source of Information	Trial registry[2]
Location	USA
Design	Randomised, placebo-controlled, parallel group design
Participants	n=382; ≥18 years old; require lipid-modifying therapy for primary or secondary prevention of cardiovascular disease; fasting LDL-C ≥130 mg/dL for primary prevention or LDL-C ≥100 mg/dL for secondary prevention (history of heterozygous FH and/or ASCVD); be statin-intolerant (unable to tolerate 2 or more statins)
Schedule	Randomised to receive bempedoic acid at a dose 180 mg tablet taken orally, daily; or receive matching placebo taken orally, daily.
Follow-up	Active treatment for 12 weeks
Primary Outcomes	Percent change in LDL-C after 12 weeks.
Secondary Outcomes	None available
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date July 2018

Trial	CLEAR Tranquility, NCT03001076; bempedoic acid and ezetimibe vs placebo and ezetimibe; phase III
Sponsor	Esperion Therapeutics
Status	Published
Source of Information	Publication[17], trial registry[3]
Location	USA
Design	Randomised, placebo-controlled, parallel group design
Participants	n=269; ≥18 years old; history of statin intolerance, were on no more than low-dose statin therapy (which could also include no statin), and required additional LDL-C lowering.
Schedule	Randomised to receive bempedoic acid at a dose 180 mg tablet taken orally, daily whilst remaining on ongoing ezetimbibe (10mg) provided in the study; or receive matching placebo taken orally, whilst remaining on ongoing ezetimibe (10mg) provided in the study.
Follow-up	Active treatment for 12 weeks
Primary Outcomes	Percent change in LDL C after 12 weeks.
Secondary Outcomes	Percent changes from baseline to week 12 in non-HDL-C, total cholesterol, apolipoprotein B, high-sensitivity C-reactive protein, triglycerides, and HDL-C.
Key Results	Bempedoic acid added to background lipid-modifying therapy that included ezetimibe reduced LDL-C by 28.5% more than placebo ($p < 0.001$; −23.5% bempedoic acid, +5.0% placebo). Significant reductions in secondary endpoints, including non-high-density lipoprotein cholesterol (−23.6%), total cholesterol (−18.0%), apolipoprotein B (−19.3%), and high-sensitivity C-reactive protein (−31.0%), were observed with bempedoic acid vs. placebo ($p < 0.001$). Bempedoic acid was well tolerated; rates of treatment-emergent adverse events, muscle-related adverse events, and discontinuations were similar in the bempedoic acid and placebo treatment groups.
Adverse effects (AEs)	Muscle-related treatment emergent adverse events (TEAE) occurred at equal frequency in the bempedoic acid and placebo treatment groups (3.3% and 3.4%, respectively). Three patients discontinued due to muscle-related TEAEs: muscle spasms and pain in extremity were experienced by one patient each in the bempedoic acid treatment group; myalgia was experienced by one patient who received placebo. Both patients in the bempedoic acid treatment group who withdrew due to muscle-related TEAEs were receiving concomitant statin therapy (pravastatin 20 mg and rosuvastatin 5 mg).
Expected reporting date	-

ESTIMATED COST

The price of bempedoic acid (monotherapy) and bempedoic acid in combination with ezetimibe is not yet known.

Ezetimibe is already marketed in the UK for the treatment of primary hypercholesterolaemia (as an adjunct to diet and statin treatment), homozygous FH (as an adjunct to diet and statin treatments), primary hypercholesterolaemia (if a statin is inappropriate or not tolerated) and homozygous sitosterolaemia (as an adjunct to diet); a pack of 28 x 10mg tablets costs £26.31.[31]

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[32]
- 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[33]
- European Society of Cardiology and European Atherosclerosis Society. Guidelines on management of dyslipidaemia. 2011[9]

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