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Bempedoic acid (monotherapy) and bempedoic acid/ezetimibe (fixed-dose combination) for primary hypercholesterolaemia or mixed dyslipidaemia

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LAY SUMMARY

Cholesterol is a type of lipid which are fatty substances vital for the normal functioning of the body. 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 (or primary) 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 and bempedoic acid combined with ezetimibe are once-daily tablets in development to treat primary hypercholesterolaemia or mixed dyslipidaemia in high risk and very high risk patients. These are patients who cannot reach the target LDL-C goals despite being treated with the maximum tolerated doses of other LDL-C lowering treatment such as statins. Bempedoic acid and ezetimibe both act in different but 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.

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TARGET GROUP

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 – adjunct to diet in combination with a statin or statin with other lipid lowering therapies[a]

DESCRIPTION

Bempedoic acid, a small molecule drug, increases low density lipoprotein (LDL) receptor-mediated clearance of LDL-cholesterol (LDL-C) by potent inhibition of adenosine triphosphate citrate lyase (ACL), an enzyme distinct from, but also complementary to, those targeted by existing lipid-modifying therapies. Bempedoic acid is a pro-drug activated specifically within the liver where it potently 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 the inhibition of those enzymes targeted by current therapies, resulting in additional lowering of LDL-C, without leading to increases in adverse events (AEs) as compared to baseline therapy. Bempedoic acid is only active in cell types that express ACSVL1, which is largely restricted to the liver. Therefore, it is believed that the myotoxicity associated with statins is unlikely to occur with bempedoic acid because it does not inhibit the cholesterol biosynthesis pathway 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 the primary target of statins.[b]

Ezetimibe selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing. 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 monotherapy and bempedoic acid with ezetimibe in a fixed-dose combination (FDC) are in phase III development (NCT03337308) for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, in patients unable to reach LDL-C goals with the maximum tolerated dose of statin therapy. They are being developed to be used as an adjunct to diet in combination with a statin, or statin with other lipid lowering therapies. In the trial, bempedoic acid is given as a 180 mg tablet once daily, and bempedoic acid with ezetimibe is administered as a FDC tablet (180 mg/ 10 mg) which is taken orally, once daily.[2,a]

Bempedoic acid monotherapy and bempedoic acid and ezetimibe FDC are not currently licensed for any indication in the EU.

Bempedoic acid as a monotherapy and in combination with ezetimibe is also 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, as an

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

adjunct to diet alone or in combination with other lipid-lowering therapies.[3,4] The effects of bempedoic acid on reducing the risk for cardiovascular events is also being studied in a phase III clinical trial.[5]

INNOVATION and/or ADVANTAGES

The current standard of care for patients with hypercholesterolaemia is statins which are capable of reducing LDL cholesterol. However, some patients with heterozygous familial hypercholesterolemia, 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. This includes patients who are not able to tolerate any meaningful dosage strength of statins. 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.[6]

Based on the complementary mechanisms of action and because both agents have 1 dosage strength, the FDC of bempedoic acid and ezetimibe should provide combined efficacy in a single oral pill without complex titration requirements and without complicating the AE profiles of the individual components.[b] Once-daily, oral therapies combined with maximum tolerated doses of lipid-modifying therapies may be of significant benefit to patients at risk of cardiovascular disease due to elevated LDL-C.[6] Therefore if licensed, bempedoic acid or the bempedoic acid and ezetimibe FDC could be additional effective treatment options for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, in patients unable to reach low-density lipoprotein cholesterol goals with the maximum tolerated statin dose, as an adjunct to diet in combination with a statin, or statin with other lipid lowering therapies.

DEVELOPER

Esperion Therapeutics, Inc

PATIENT GROUP

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.[7] Along with other cardiovascular risk factors, dyslipidaemia may lead to the development of atherosclerosis and cardiovascular disease (CVD).[8]

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.[9] 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 low density lipoprotein (LDL) cholesterol.[10] Elevated LDL-C levels are associated with increased vascular inflammation and atherosclerosis.[11,12,13,14]

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. However, several other types of dyslipidaemias also appear to predispose patients to premature CVD. The atherogenic lipid triad is connected to insulin resistant states or type 2 diabetes, and is commonly seen in premature CVD. It consists of elevated very low density lipoprotein (VLDL) particles manifesting in clinical laboratory measurements as mildly elevated triglycerides, increased small density LDL particles, and reduced HDL-C levels, often accompanied by raised levels of apolipoprotein B (APOB).[8]

Hypercholesterolaemia is characterised by high cholesterol concentration in the blood, including elevated LDL. 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.[15] FH has an autosomal dominant pattern of inheritance caused primarily by mutations in the gene encoding the LDL receptor (LDLR). Mutations occur less commonly in the APOB and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes but have similar functional consequences. In FH, the LDL receptor pathway results in a reduced clearance of LDL-C from plasma, which increases the plasma concentration of LDL and the total cholesterol.[16] FH can lead to the early development of atherosclerosis and coronary heart disease,[17] 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.[18] 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 the atherosclerosis can cause angina, myocardial infarction and stroke.[15]

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)[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.[15] 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.[19]

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 majority of mortality in England and is the leading cause of death in the UK.[26] It has been estimated that nearly 80% of patients with existing ASCVD who are taking a statin are not achieving adequate LDL-C reductions.[20]

In 2016-17, the prevalence of CVD was approximately 5.9 million in the England.[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] 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.[10]

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.[23]

PATIENT PATHWAY

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 and POLICY GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- European Society of Cardiology/European Atherosclerosis Society. European guidelines on cardiovascular disease prevention in clinical practice. 2016.[24]
- 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.[25]
- European Society of Cardiology and European Atherosclerosis Society. Guidelines on management of dyslipidaemia. 2011.[8]

CURRENT TREATMENT OPTIONS

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.[15]

Current lipid modification therapy options for hyperlipidaemia in the primary prevention of CVD include:[15,26,27]

- Statin therapies licensed for the use in the UK include:
    - Atorvastatin
    - Simvastatin
    - Pravastatin
    - Fluvastatin
    - Rosuvastatin

- 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:[26]

- Statins.
- 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.

EFFICACY and SAFETY	
Trial	**NCT03337308,** bempedoic acid and ezetimibe FDC vs bempedoic acid vs ezetimibe vs placebo; phase III
Sponsor	Esperion Therapeutics
Status	Ongoing
Source of Information	Trial registry[2]
Location	USA
Design	Randomised, double-blind, controlled, parallel group study
Participants	n=350; ≥ 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 atherosclerotic cardiovascular disease); treated with maximally tolerated statin therapy at stable dose for at least 4 weeks prior to screening
Schedule	Randomised to receive: • Bempedoic acid + ezetimibe FDC 180 mg/10 mg tablets taken orally once daily for 12 weeks and placebo tablet or capsule to match bempedoic acid + ezetimibe FDC 180 mg/10 mg tablet, or bempedoic acid 180 mg tablet, or ezetimibe 10 mg capsule • Bempedoic acid 180 mg tablets taken orally once daily for 12 weeks or placebo tablet and capsule to match bempedoic acid + ezetimibe FDC 180 mg/10 mg tablet, or bempedoic acid 180 mg tablet, or ezetimibe 10 mg capsule • Ezetimibe 10 mg overencapsulated tablets taken orally once daily for 12 weeks or placebo tablet and capsule to match bempedoic acid + ezetimibe FDC 180 mg/10 mg tablet, or bempedoic acid 180 mg tablet, or ezetimibe 10 mg capsule • Placebos to match identical bempedoic acid + ezetimibe FDC 180 mg/10 mg tablet, and identical bempedoic acid 180 mg tablet, or identical ezetimibe 10 mg capsule, taken orally, once daily for 12 weeks
Follow-up	Active treatment for 12 wks
Primary Outcomes	Percent change in LDL-C from baseline through 12 weeks.
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2018

ESTIMATED COST and IMPACT

COST

Ezetimibe costs £26.31 for 28 x 10mg tablets.[28]

The price of bempedoic acid and bempedoic acid and ezetimibe FDC is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: *reduced LDL-C levels and risk of CVD*[c]

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *LDL-C reductions and reductions in CVD events may lead to reduced other costs*[c]

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

[c] Company information

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