REVIEW

Evaluating bempedoic acid for the treatment of hyperlipidaemia

Peter Penson[1], Mary McGowan[2,3], Maciej Banach[4-6*]

School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [2]Esperion Therapeutics, Inc., Ann Arbor, MI, USA; [3] Section of Cardiology, Dartmouth-Hitchcock Heart & Vascular Center, Lebanon, NH;[4]Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland; [5]Healthy Aging Research Centre (HARC), Lodz, Poland; [6]Polish Mother's Memorial Hospital Research Institute, Lodz, Poland.

***Corresponding author:** Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA, Head, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113; 90-549 Lodz, Poland. **Phone:** +48 42 639 37 71; **Fax:** +48 42 639 37 71;**E-mail:** maciejbanach@aol.co.uk

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ABSTRACT:

Introduction: Despite the effectiveness of statins in the treatment of lipid disorders, residual risk still exists, and hitherto studies where additional drugs were added to statin therapy have been mainly negative or the outcomes were very modest. Therefore there is still a need for new and effective oral agents in the combination therapy of lipid disorders.

Areas Covered: The review covers the current state of knowledge on the mechanism of action of bempedoic acid (ETC-1002) and results from recent clinical studies.

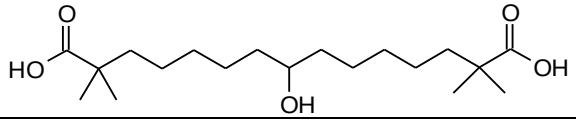
Expert Opinion: ETC-1002 is a novel oral lipid-lowering therapy. The reduction of both low-density lipoprotein cholesterol (LDL-C) and high sensitivity C-reactive protein (hsCRP) demonstrated by ETC-1002 in clinical trials suggests that agent may have the potential for CV risk reduction. Adverse effects of current lipid-lowering agents can be dose-limiting, and combination approaches to lipid-lowering may often be utilized for optimal CV risk reduction. Because of this, new lipid-modulating drugs are urgently required. ETC-1002 has a unique mechanism of action (adenosine triphosphate-citrate lyase inhibition). It has been shown to be safe in combination with statins as well as ezetimibe, and appears to effectively lower LDL-C and has the potential to reduce the risk of muscle-related adverse events, which can limit the utilization and effectiveness of statin therapy.

Keywords: ETC-1002, Bempedoic acid, hyperlipidaemia, atherosclerosis, cardiovascular disease.

ARTICLE HIGHLIGHTS:

1. Bempedoic acid (ETC-1002) is a novel lipid-lowering drug with a unique mechanism of action.
2. Bempedoic acid is a prodrug of bempedoic acid-CoA, which reduces cholesterol production by inhibition of adenosine triphosphate-citrate lyase. Conversion of bempedoic acid to the active form occurs preferentially in the liver.
3. Bempedoic acid reduces LDL-C in a wide variety of hypercholesterolaemic populations including patients with cardiovascular disease (CVD), type 2 diabetes, mildly elevated blood pressure, elevated and normal triglyceride concentrations
4. In all studies to date, bempedoic acid has been shown to reduce hsCRP, a marker of inflammation with respect to CVD.
5. Bempedoic acid has an additive effect upon LDL-C lowering when combined with existing lipid-lowering agents (ezetimibe and statins).

Drug Summary:

Drug Name:	Bempedoic acid
Phase:	2-3
Indication:	Hyperlipidaemia
Mechanism of Action:	Inhibition of adenosine triphosphate-citrate lyase
Route of Administration:	Oral
Chemical Structure:	8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid 
Pivotal trials:	ETC1002-040 (NCT02666664, Ongoing) Randomized Controlled Cardiovascular outcomes trial with approximately 1950 participants ETC1002-043 (Planned) Randomized Controlled Cardiovascular outcomes trial with approximately 12600 participants

ABBREVIATIONS:

ACL	Adenosine triphosphate-citrate lyase
ACS	Acyl-CoA synthetase
ACSVL1	Very long-chain acyl-CoA synthetase
ASCVD	Atherosclerotic cardiovascular disease
CLEAR	**C**holesterol **L**owering via B**E**mpedoic acid, an **A**CL-inhibiting **R**egimen
CHD	Coronary Heart Disease
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
EMA	European Medicines Agency
FDA	(United States) Food and Drug Administration
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
hsCRP	High sensitivity C-reactive protein
LDL-C	Low-density lipoprotein Cholesterol
Lp(a)	Lipoprotein(a)
Non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
SWOT	Strength, Weakness, Opportunity, Threat
TC	Total cholesterol
TG	Triglycerides

1. Overview of the market

Reduction in risk of cardiovascular disease (CVD) morbidity and mortality *via* reduction of low-density lipoprotein cholesterol (LDL-C) has been shown to be effective in both primary [1] and secondary [2] prevention of CV events [3]. This approach became possible with the introduction of statins, drugs that target the mevalonate pathway downstream of adenosine triphosphate-citrate lyase (ACL) by inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-limiting step in cholesterol biosynthesis. This has been a remarkably successful and consistent approach to cardiovascular disease risk reduction. The Cholesterol-Treatment Trialists' collaborators performed a meta-analysis of 14 randomized controlled trials (RCTs) and concluded that lowering plasma concentrations of LDL-C by 1 mmol/L (38.7 mg/dl) reduced the risk of major coronary events by 23% over 5 years. The greatest benefit was seen in those who had had a previous cardiovascular (CV) event, but a substantial reduction in CVD was also observed in a primary prevention population [4].

Recent developments have enabled more substantial reductions in plasma LDL-C, an approach that would appear to result in a further reduction of CV risk. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) investigated combination therapy with simvastatin and ezetimibe in secondary prevention. The combination led to lower LDL-C levels (53.7 vs 69.5 mg/dL) than simvastatin monotherapy, and importantly this translated to reduced risk of the primary endpoint, which was a composite of cardiac events (hazard ratio [HR] 0.936 [0.89 to 0.99]) [5]. However, surprisingly, despite these positive and significant results the US Food and Drug Administration (FDA) did not approve ezetimibe for use as an addition to statin therapy for reduction of CV events in patients with coronary heart disease (CHD) [6, 7].

A new class of lipid lowering agents, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-i) have recently been approved for LDL-C lowering in multiple countries. They show a substantial reduction in LDL-C levels. The ODYSSEY-LONG TERM trial, which recruited participants with heterozygous familial hypercholesterolemia (HeFH), CHD or a risk equivalent, demonstrated substantial reductions in LDL-C after treatment with alirocumab, a monoclonal antibody inhibitor of PCSK9 protein, when used with a statin [8, 9]. These LDL-C lowering results complement those of the OSLER study, which utilized evolocumab, another PCSK9 inhibitor [10]. Both studies showed significant reduction of CV events with PCSK9 inhibitors (however it is worth mentioning that these studies were neither designed nor powered to investigate CV outcomes) and confirmed the safety of LDL-C reduction, to levels even below 25 mg/dL [6, 7]. The results of the cardiovascular outcomes trials (CVOT) with these agents (FOURIER, ODYSSEY OUTCOMES) are expected in 2017 and 2018 [11, 12].

However, the effectiveness of LDL-C lowering therapy in clinical practice has been limited by a number of factors, including poor adherence to statin therapy, statin discontinuation [13] and statin intolerance [14] and residual risk despite achieving therapeutic LDL-C targets [6, 15]. Statin monotherapy or combinations of currently available drugs are unlikely to achieve optimal concentrations of LDL-C in all patients, especially those who are at high CV risk [16]. Despite the fact that statins are very well tolerated, they do have well documented adverse effects, mainly muscle-related adverse events, and PCSK9 inhibitors require subcutaneous injection, which may not be acceptable or convenient for all patients. Lipid reduction by ezetimibe as monotherapy is limited [17]. Thus, despite the benefits conferred by these drugs, there is an urgent clinical need for new LDL-C lowering therapies, which can be demonstrated to significantly reduce elevated

LDL-C levels and limit adverse effects, either as monotherapy or in combination with existing drugs. Bempedoic acid shows early promise in this regard.

2. Introduction to Bempedoic Acid

Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid, ETC-1002, developed by Esperion Therapeutics Inc., is a novel lipid regulating drug with a unique mechanism of action. It is a prodrug that is converted to bempedoic acid-CoA - a competitive inhibitor of the enzyme ACL. Conversion of bempedoic acid to the active form (ETC-1002 CoA) occurs preferentially in the liver [18]. ACL is the enzyme responsible for hepatic production of cytosolic acetyl-coenzyme A, the precursor of the mevalonate pathway of cholesterol biosynthesis. The predominant biochemical manifestation of bempedoic acid therapy is an increase in low density lipoprotein (LDL)-receptor activity and a subsequent reduction in plasma concentrations of LDL-C [18].

The mechanism of action of bempedoic acid, as understood from preclinical studies and the results of clinical trials, was extensively discussed in a review published in 2014 [19], and, more recently, presented at the Scientific Sessions of the American Heart Association in 2015. The definitive mechanism of action of bempedoic acid has just been published [20]. New clinical evidence and an improved understanding of the mechanism of action of bempedoic acid have provoked this update. We aim to give an overview of all aspects of this promising new agent, with a particular focus on the results of Phase 2 clinical trials and recent experimental studies.

2.1. Pharmacology and mechanism of action of bempedoic acid

The predominant biochemical manifestations of bempedoic acid administration are an increase in LDL receptor activity and consequent reduction in the plasma concentration of LDL-C [18]. In relation to its LDL-C lowering effect, bempedoic acid is a prodrug of ETC-1002-Coenzyme A (ETC-1002-CoA). ETC-1002-CoA acts as a competitive inhibitor of the enzyme adenosine triphosphate-citrate lyase and reduces the production of cytosolic acetyl-coenzyme A, the precursor of the mevalonate pathway of cholesterol biosynthesis [18]. ACL is a unique target for LDL-C and CV risk reduction because it produces precursors required for both fatty acid and cholesterol synthesis [21] (**Figure 1**). Genetic inhibition of ACL has been shown to up-regulate LDL receptor expression and activity in McArdle cells [18]. Polymorphisms of ACLY, the gene encoding ACL have been linked with varying growth traits in cattle [22] and altered plasma triglyceride responses to fish-oil supplementation in humans [23].

The mechanism by which bempedoic acid is converted to the active form, ETC-1002-CoA, has been extensively investigated in preclinical experiments [24]. It has been demonstrated that bempedoic acid is converted into ETC-1002-CoA by hepatic acyl-CoA synthetase (ACS) [18], a family of enzymes, which catalyse the CoA thioesterification of fatty acids and thereby regulate the distribution and trafficking of fatty acids into complex lipids [25]. In particular, very long-chain acyl-CoA synthetase 1 (ACSVL1) has been identified as the specific isoform of ACS responsible for activation of bempedoic acid to ETC-1002-CoA [18]. ETC-1002-CoA formation correlates with ACSVL1 expression in human liver subcellular fractions, and genetic silencing of ACSVL1 with small interfering RNAs (siRNAs) has been shown to prevent formation of bempedoic acid-CoA in McArdle cells. ACSVL1 is highly expressed in human liver microsomes, only modestly expressed in kidney, and has not been detected in skeletal muscle cells [18]. Thus,

the distribution of ACSVL1 (and therefore the sites of ETC-1002-CoA activity) would appear to be ideal to allow perturbation of hepatic cholesterol synthesis, with minimal effects in other tissues [18]. In particular, the absence of ASCVL1 (and therefore ETC-1002-CoA) in skeletal muscle may allow effective LDL-C-lowering with reduced risk of muscle-related adverse events. These events have been associated with statin therapy, and may result from the depletion in skeletal muscle of mevalonate pathway products, downstream of HMG-CoA-reductase [26-29]

3. Clinical efficacy and safety of bempedoic acid

Clinical trials investigating the efficacy and safety of bempedoic acid have been conducted, or are ongoing in a variety of populations including patients with hypercholesterolaemia and either normal or elevated triglycerides [30,31], patients with hypercholesterolaemia and type 2 diabetes mellitus [32], patients with hypercholesterolaemia and statin intolerance [33], hypercholesterolaemia and hypertension [34]. Additionally, bempedoic acid has been studied in combination with statins [35,36] or ezetimibe [37] (**Table 1**). The overall Phase 3 program evaluating the safety and efficacy of bempedoic acid is referred to as the Cholesterol Lowering via BEmpedoic Acid, an ACL-Inhibiting Regimen (CLEAR). Specifically, CLEAR Harmony (Study 1002-040) is investigating the long-term safety of bempedoic acid in patients with atherosclerotic cardiovascular disease (ASCVD) and/or HeFH [38]. The effects of bempedoic acid on lipids and lipoproteins in phase 2 clinical studies reported to date are summarized below.

3.1. Efficacy and safety of bempedoic acid in patients with elevated blood cholesterol and either normal or elevated triglycerides

Ballantyne *et al.* conducted a phase 2 clinical trial (ETC-1002-003, NCT01262638) to investigate the safety and efficacy of bempedoic acid in a group of 177 patients with normal (<150 mg/dL) and elevated (150 to <400 mg/dL) triglycerides and hypercholesterolaemia who were randomized to receive placebo or bempedoic acid 40mg, 80mg or 120mg daily for 12 weeks [31]. The baseline characteristics of all groups were very similar: mean age 56-59 years, and baseline mean LDL-C was between 163 mg/dL and 170 mg/dL for all groups [31]. Treatment with bempedoic acid led to mean reductions of LDL-C by 26.6±2.2% in the 120mg bempedoic acid group compared to a 2.1±2.2% reduction in placebo, a statistically significant difference ($p<0.001$). The reduction in LDL-C appeared to occur in the first two weeks of treatment and to stabilize thereafter. Triglyceride status (normal or elevated) did not appear to influence LDL-C lowering [31]. Non-HDL-C and apolipoprotein B (apoB) reductions were similar in magnitude to LDL-C reductions; LDL particle number, an emerging marker of CV risk [39-42], decreased, and a statistically significant increase in HDL particle number was observed at the highest and lowest doses. Lipoprotein(a) [Lp(a)] did not appear to be altered by bempedoic acid. No safety concerns have emerged in this trial, or any other trial to date [31].

3.2. Bempedoic acid in patients with type 2 diabetes mellitus

Gutierrez *et al.* assessed the efficacy and safety of bempedoic acid in patients with type-2 diabetes mellitus (DMt2), a population at very high risk for developing CVD. The trial (ETC-1002-005, NCT01607294) involved 60 DMt2 patients with hypercholesterolaemia who were randomised to receive placebo for four weeks or bempedoic acid (80mg/day for two weeks, then 120 mg/day for 2 weeks) [32]. LDL-C was reduced by 39% (95% confidence interval [CI]: 46.2, 31.7, $p<0.0001$) compared to placebo, reductions were also seen for non-HDL-C: 31.4% (38.0-

24.8, p=0.0001) and total cholesterol (by 24.6%, 29.9-19.4, p<0.001) compared to placebo. Treatment with bempedoic acid was associated with a 40.5% median reduction in high sensitivity C-reactive protein (hsCRP), compared with 11.0% for placebo (p=0.0011). There was no statistically significant difference between groups in terms of HDL-C, triglycerides, free fatty acids or fasting insulin suggesting a neutral effect on these parameters. Additionally, unlike what has been seen in some statin studies [43,44] the impact of bempedoic acid on glucose was neutral [32].

3.3. Efficacy and safety of bempedoic acid in patients with statin intolerance

Statin intolerance worsens therapy adherence, increases drug discontinuation and can limit the effectiveness of CV risk reduction [14,28,45] and thus, alternative strategies for lipid-lowering are required in patients who suffer adverse effects on statin therapy. Thompson *et al.* investigated the effects of bempedoic acid in 56 hypercholesterolaemic patients with statin intolerance (ETC-1002-006, NCT01751984). Statin intolerance was defined as muscle-related adverse effects that occurred upon treatment with at least one statin which resolved within four weeks of discontinuation. The trial was conducted over 8 weeks. Patients were randomized to receive either placebo (n=19) or an initial dose of 60mg bempedoic acid, increased at 2 week intervals to reach a 240 mg daily dose (n=37) [33]. Consistent with previous studies, [31,32] bempedoic acid reduced LDL-C 28.7% more than placebo (95%CI: -35.4 to -22.1; p<0.0001). Similar statistically significant reductions in non-HDL-C and total cholesterol were observed. ApoB was reduced by 19.7±2.6% in bempedoic acid treated patients compared with 4.4±3.8% in placebo (p=0.0019) [33]. And likewise, hsCRP was reduced significantly in the treated vs placebo group (p=0.0022). 62% of patients randomized to bempedoic acid achieved LDL-C goals, compared with none in the

placebo group ($p<0.0001$). There was no statistically significant difference between the groups in terms of HDL-C, triglycerides, apoA-I, Lp(a) or free fatty acids.

Adverse events were reported by 79% of patients treated with placebo, and 70% treated with bempedoic acid. These led to discontinuation in 16% of patients in the placebo group and 14% in bempedoic acid group. A similar percentage of placebo and bempedoic acid treated patients (32 vs 27%) reported muscle adverse effects, and 16% of placebo treated patients withdrew due to muscle-related side-effects, whereas importantly there were no discontinuations because of muscle-related side effects in the bempedoic acid group [33].

3.4. Bempedoic acid and ezetimibe combined therapy

Combination therapy with ezetimibe (which reduces cholesterol absorption by blocking Niemann-Pick C1-like 1 proteins on intestinal epithelial cells) [6] and bempedoic acid (which reduces hepatic cholesterol biosynthesis leading to up-regulation of the LDLR), is a rational multi-target approach to lipid lowering. This tactic has been shown to lower LDL-C by up to 48%. Ezetimibe is commonly used in statin intolerant patients [46], however, its ability to lower LDL-C as a monotherapy is limited. Thus the combined use of ezetimibe and bempedoic acid in statin intolerant patients has potential value in terms of improved LDL-C goal attainment.

A study evaluating the combination of bempedoic acid (120 or 180 mg daily) with ezetimibe (10mg daily) was compared with monotherapy of each drug in a 12 week trial, which randomized 349 patients, and included patients with good adherence to statin therapy and statin intolerant patients (ETC-1002-008, NCT01941836). In this study statin intolerance was defined as the inability to tolerate at least two statins, including one statin at the lowest approved dose due to muscle-related symptoms such as pain, aches, weakness, or cramping that began or increased

during statin therapy and resolved when statin therapy was discontinued. Monotherapy with bempedoic acid resulted in very similar effects on lipid profiles to those seen in the studies described above [31-33]. LDL-C was reduced by 27.5±1.3% (least-squares mean ± standard error) by the 120mg dose. The 180 mg dose resulted in a reduction of 30.1±1.3%. Reductions were also seen in apoB, LDL particle number, total cholesterol and non-high-density lipoprotein cholesterol, (non-HDL-C).

In common with previous trials [31-33], use of bempedoic acid was associated with a reduction in hsCRP (by 30.1% with 120mg and by 40.2% with 180mg) [37]. Ezetimibe monotherapy was also associated with reductions of LDL-C, LDL particle number, total cholesterol and non-HDL cholesterol, but in all cases these reductions were smaller than the reductions achieved by bempedoic acid, and the differences between the ezetimibe group and the bempedoic acid groups were statistically significant. Ezetimibe was associated with an increase in HDL-C of 5.0±1.4%. Combined therapy led to greater reductions in LDL-C - 120 mg bempedoic acid + 10 mg ezetimibe reduced LDL-C by 43.1±2.6% and 180 mg bempedoic acid + 10 mg ezetimibe by 47.7±2.8% ($p<0.0001$). LDL-C lowering was very similar in subgroups of statin tolerant and statin intolerant patients. Similarly, the reductions in LDL particle number, apoB, total cholesterol, non-HDL-C were greater in all cases than with either monotherapy treatment arm. This suggests that the beneficial effects of ezetimibe and bempedoic acid on LDL-C lowering can be additive. The combination of ezetimibe and bempedoic acid 180 mg (n=24) produced a reduction in hsCRP of 25.6%, while the reduction in hsCRP with bempedoic acid 180 mg (n=100) monotherapy was 40.2%. It is unclear if the less robust reduction in hsCRP observed with the combination is due to variability of hsCRP in this much smaller treatment arm [35]. The frequency of adverse events resulting in discontinuation of study drug was 3.0% for bempedoic acid 120 mg, 6.0% for

bempedoic acid 180 mg, 8.0% for ezetimibe, 8.0% for bempedoic acid 120 mg + ezetimibe and 4.0% for bempedoic acid 180 mg + ezetimibe. As with other safety measures, rates of muscle-related adverse events were similar across all treatment groups. These results raised no safety concerns regarding the use of bempedoic acid [37].

3.5. Bempedoic acid and statin combined therapy

The efficacy of combination therapy with statins and bempedoic acid has been investigated in two completed studies [35,36] and it is the subject of one ongoing [47] study. A small study (ETC-1002-007, NCT01779453) was conducted in a patient population taking atorvastatin 10mg at baseline and either placebo (n=19) or bempedoic acid titrated up to 240mg/day over 8 weeks (n=42) [35]. Compared with placebo, bempedoic acid was associated with an additional reduction of LDL-C of 22% (95%CI: 11.4-32.7%). The difference between the groups was statistically significant (p=0.0001). With respect to hsCRP, the reduction in the placebo treated group was 9% compared to a 23.5% reduction in hsCRP in the bempedoic acid treated patients (p=0.33). No safety concerns related to treatment with bempedoic acid were noted [35].

A larger randomized controlled trial (ETC-1002-009, NCT02072161) investigated the effects of 120mg, 180mg of bempedoic acid or placebo in 134 patients who had been treated with one of a range of statin regimens atorvastatin 10 or 20 mg, simvastatin 5, 10, or 20 mg, rosuvastatin 5 or 10 mg or pravastatin 10, 20, or 40 mg for at least 3 months before the trial began [36]. LDL-C was reduced by 4.2±4.2% in placebo treated patients and by 17.3±4.0% and 24.3±4.2% in patients treated with 120mg and 180mg respectively. These reductions were statistically different than placebo at p values of <0.01 and <0.001 respectively. Consistent with previous studies, reductions in hsCRP were seen following bempedoic acid treatment (although not statistically significant,

hsCRP was unchanged in the placebo and reduced by 21.8% and 29.8% in 120mg [p=0.26] and 180mg [p=0.08] groups respectively) [36]. Similar, to all the other trials described above, the adverse effect profile of bempedoic acid was very similar to the placebo group in this trial [36].

3.6. Ongoing research

It has been previously observed that bempedoic acid reduced blood pressure (BP) in a post-hoc analysis of patients with mildly elevated blood pressure [31]. A recently completed double blind placebo controlled trial (ETC-1002-014, NCT02198098) investigated the effects on LDL-C and BP of 180mg bempedoic acid over 6 weeks [34]. Patients treated with 180 mg of bempedoic acid had a 21 % reduction in LDL-C ($p < 0.0001$), and a 24 % reduction as compared to placebo ($p < 0.0001$), which increased by 3%. Bempedoic acid reduced hsCRP by 25% from baseline and 44 % vs placebo ($p < 0.0001$ for both). There was a neutral effect on blood pressure and no muscle-related adverse events (AEs) [48].

Following observations of an incremental LDL-C lowering effect of bempedoic acid on low and moderate dose statin therapy [35,36], an ongoing study (ETC-1002-035, NCT02659397), enrolling 60 patients is investigating the safety, pharmacokinetics and pharmacodynamics of adding bempedoic acid therapy to high dose (atorvastatin 80mg) statin therapy [47].

Esperion has also launched a programme of Phase 3 studies called ‘Cholesterol Lowering via BEmpedoic acid, an ACL-inhibiting Regimen (CLEAR)’. The first Phase 3 study, CLEAR Harmony (ETC-1002-040, NCT02666664) is a multinational double blind study designed to investigate the effects of bempedoic acid in patients with high cardiovascular risk and elevated LDL-C that is not controlled by maximally-tolerated lipid-modifying therapy. The primary endpoint is the frequency of treatment-related adverse effects, and lipid parameters and hsCRP are

included as secondary endpoints. 1950 patients will be enrolled in multiple centers in the US and Europe, and will receive a daily dose of 180 mg bempedoic acid or placebo. Importantly, this trial is recruiting patients with diagnosed ASCVD and/or HeFH, thus it will enable evaluation of bempedoic acid in patients at the very highest levels of risk [38].

Another study - A randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant (ETC-1002-043) will soon be initiated [49]. This trial will include approximately 12,600 adult male and female patients ≥18 years of age with inability to tolerate two or more statins, one at a low dose, due to adverse safety effects that started or increased during statin therapy, and resolved or improved when statin therapy was discontinued. Low dose statin therapy (LDST) is defined as less than an average starting daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. The investigators assumed that patients who tolerate very low dose statin therapy (less than LDST as outlined above) are considered to be intolerant to that low dose statin and may qualify for the study. Patients may continue taking very low dose statin therapy throughout the study provided that it is stable (used for at least four weeks prior to screening) and well tolerated. In this double blind study patients will be randomized 1:1 to either bempedoic acid (180 mg) or placebo once daily. The primary objective in this study is to evaluate whether long-term treatment with bempedoic acid reduces the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for CVD who are statin intolerant [49].

4. Conclusion

The reduction of LDL-C (as well as non-HDL-C, apoB and total cholesterol) and hsCRP demonstrated as monotherapy and in combination with statins and ezetimibe by bempedoic acid in phase 2 clinical trials suggest that bempedoic acid has potential for CV risk reduction by modulation of both lipids and inflammation. Early results would suggest that this can potentially be achieved with a reduced risk of muscle-related adverse events, which might limit the utilization and effectiveness of statin therapy. Table 2 is a SWOT analysis relating to the potential use of bempedoic acid. A CVOT is planned to determine whether the potential of bempedoic acid is realized in the reduction in risk of CV events and death.

5. Expert Opinion

The effects of bempedoic acid on the lipid profile and other biochemical parameters such as hsCRP would suggest that it has the potential to reduce the risk of CVD in a variety of situations and in combination with other lipid-lowering agents. Outcomes data are now required in order to determine whether CV events are reduced by therapy with bempedoic acid. A planned cardiovascular outcome trial (CVOT) will determine the effects of bempedoic acid on the risk of CV events and mortality. Previously published trials with bempedoic acid were associated with low rates of muscle related adverse effects. Larger clinical studies with bempedoic acid will investigate these adverse effects and also assess the incidence of less common adverse events. Ongoing and future trials may be able to answer questions that current data cannot. Large well-powered trials may allow subgroup analyses of the results, such that clinical outcomes can be investigated separately in males and females and in different racial groups, in younger and older subjects, and in the patients with concrete concomitant conditions. Most studies conducted thus far have administered bempedoic acid on a background of statin therapy. A head-to-head clinical

trial comparing bempedoic acid against statin therapy, and especially against other lipid lowering drugs, which are add-on therapy to statins, would allow a comparison the effects of these drugs on lipid markers, hsCRP, and ultimately clinical outcomes.

If the results of ongoing trials show acceptable results in terms of safety and efficacy, bempedoic acid would be well placed to be used as an add-on therapy in patients with lipid profiles which are inadequately controlled on standard therapy. The results of the IMPROVE-IT trial have demonstrated the clinical benefit of lipid-lowering beyond that which can be achieved by a statin alone, and therefore this is an important clinical indication. New therapeutic agents are needed because of the dose-limiting adverse effects of statins and other current agents. In this setting, bempedoic acid has advantages over PCSK9 inhibitors despite the fact that it does not lower plasma cholesterol concentrations to the same extent. Bempedoic acid is bioavailable after oral administration, and thus does not require patients to undergo injections. Bempedoic acid is a small molecule and manufacture is therefore likely to be less expensive than the PCSK9 inhibitor monoclonal antibodies. Bempedoic acid appears to be effective in a multitude of hypercholesterolaemic patient types: across a range of triglyceride concentrations, in patients with type 2 diabetes mellitus, in patients with hypertension, as monotherapy and in combination with statins and with ezetimibe. This versatility may mean that bempedoic acid may prove to be a useful addition to lipid-lowering therapy for a large number of patients.

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REFERENCES:

1. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301-7

2. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-9

3. Hobbs FD, Banach M, Mikhailidis DP, et al. Is statin-modified reduction in lipids the most important preventive therapy for cardiovascular disease? A pro/con debate. BMC Med. 2016;14:4

4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-78

5. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372:2387-97

6. Serban MC, Banach M, Mikhailidis DP. Clinical implications of the IMPROVE-IT trial in the light of current and future lipid-lowering treatment options. Expert Opin Pharmacother. 2016;17:369-80

7. Banach M, Nikolic D, Rizzo M, et al. IMPROVE-IT: what have we learned? Curr Opin Cardiol. 2016;31:426-33

8. Saleheen D, Scott R, Javad S, et al. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. Lancet Diabetes Endocrinol. 2015;3:507-13

9. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489-99

10. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500-9

11. Banach M, Aronow WS, Serban MC, et al. Lipids, blood pressure and kidney update 2015. Lipids Health Dis. 2015;14:167

12. Dragan S, Serban MC, Banach M. Proprotein convertase subtilisin/kexin 9 inhibitors: an emerging lipid-lowering therapy? J Cardiovasc Pharmacol Ther. 2015;20:157-68

13. Banach M, Serban MC. Discussion around statin discontinuation in older adults and patients with wasting diseases. J Cachexia Sarcopenia Muscle. 2016;7:396-9

14. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Expert Opin Drug Saf. 2015;14:935-55

15. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. Curr Atheroscler Rep. 2012;14:1-10

16. Katsiki N, Nikolic D, Montalto G, et al. The role of fibrate treatment in dyslipidemia: an overview. Curr Pharm Des. 2013;19:3124-31

17. Patel J, Martin SS, Banach M. Expert opinion: the therapeutic challenges faced by statin intolerance. Expert Opin Pharmacother. 2016;17:1497-507

18. Pinkosky SL, Newton RS, Birch CM, et al. Abstract 17608: Identification of a Tissue-specific Very Long-chain Acyl-CoA Synthetase Involved in the Inhibition of ATP-Citrate Lyase (ACL) by ETC-1002: A Novel Mechanism for Cholesterol Biosynthesis Inhibition in the Liver. Circulation. 2015;132:A17608

19. Nikolic D, Mikhailidis DP, Davidson MH, et al. ETC-1002: a future option for lipid disorders? Atherosclerosis. 2014;237:705-10.

20. Pinkosky SL, Newton RS, Day EA, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nature Commun 2016;7:13457.

21. Lemus HN, Mendivil CO. Adenosine triphosphate citrate lyase: Emerging target in the treatment of dyslipidemia. Journal of clinical lipidology. 2015;9:384-9.

22. Li MN, Guo X, Bao PJ, et al. Association of genetic variations in the ACLY gene with growth traits in Chinese beef cattle. Genet Mol Res. 2016;15

23. Bouchard-Mercier A, Rudkowska I, Lemieux S, et al. Polymorphisms, de novo lipogenesis, and plasma triglyceride response following fish oil supplementation. J Lipid Res. 2013;54:2866-73

24. Pinkosky SL, Filippov S, Srivastava RA, et al. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. J Lipid Res. 2013;54:134-51. Epub 2012/11/03

25. Melton EM, Cerny RL, Watkins PA, et al. Human fatty acid transport protein 2a/very long chain acyl-CoA synthetase 1 (FATP2a/Acsvl1) has a preference in mediating the channeling of exogenous n-3 fatty acids into phosphatidylinositol. J Biol Chem. 2011;286:30670-9

26. Parker BA, Gregory SM, Lorson L, et al. A randomized trial of coenzyme Q10 in patients with statin myopathy: rationale and study design. Journal of clinical lipidology. 2013;7:187-93

27. Lawrence J, Moyer C, Ameri M, et al. Abstract 13907: Statin-Induced Myopathy is Mediated by Isoprenoid Depletion and is Independent of Serum Cholesterol Levels. Circulation. 2014;130:A13907

28. Gluba-Brzozka A, Franczyk B, Toth PP, et al. Molecular mechanisms of statin intolerance. Arch Med Sci. 2016;12:645-58

29. Muntean DM, Thompson PD, Catapano AL, et al. Statin-associated myopathy and the quest for biomarkers: Can we effectively predict statin-associated muscle symptoms? Drug Discovery Today. 2016; in press; doi: 10.1016/j.drudis.2016.09.001

30. Ballantyne CM, Davidson M, MacDougall D, et al. ETC-1002 lowers LDL-C and beneficially modulates other cardio-metabolic risk factors in hypercholesterolemic subjects with either normal or elevated triglycerides. Journal of the American College of Cardiology. 2012;59:E1625-E

31. Ballantyne CM, Davidson MH, Macdougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol. 2013;62:1154-62. Epub 2013/06/19

32. Gutierrez MJ, Rosenberg NL, Macdougall DE, et al. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol. 2014;34:676-83. Epub 2014/01/05

33. Thompson PD, Rubino J, Janik MJ, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. Journal of clinical lipidology. 2015;9:295-304. Epub 2015/06/16

34. Esperion Therapeutics. Evaluation of ETC-1002 in Patients With Hypercholesterolemia and Hypertension : Clinical trial.gov protocol 2015. Available from: https://clinicaltrials.gov/show/NCT02178098

35. Newton RS, Ballantyne CM, Thompson PD, et al. ETC-1002 lowers LDL-cholesterol and is well tolerated in hypercholesterolaemic patients across four phase 2a studies. NLA Scientific Sessions; 2014 May 1-4 2014

36. Ballantyne CM, McKenney JM, MacDougall DE, et al. Effect of ETC-1002 on Serum Low-Density Lipoprotein Cholesterol in Hypercholesterolemic Patients Receiving Statin Therapy. Am J Cardiol. 2016;117:1928-33

37. Thompson PD, MacDougall DE, Newton RS, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. Journal of clinical lipidology. 2016;10:556-67

38. Esperion Therapeutics. Evaluation of Long-Term Safety and Tolerability of ETC-1002 in High-Risk Patients With Hyperlipidemia and High CV Risk : Clinical trial.gov protocol 2016. Available from: https://clinicaltrials.gov/show/NCT02666664

39. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. Journal of clinical lipidology. 2007;1:583-92

40. Gondeck K. LDL particle number and size. Measurement as a strategy for CAD prevention. Adv NPs PAs. 2012;3:26-8

41. Matyus SP, Braun PJ, Wolak-Dinsmore J, et al. NMR measurement of LDL particle number using the Vantera Clinical Analyzer. Clin Biochem. 2014;47:203-10

42. Kucera M, Oravec S, Hirnerova E, et al. Effect of atorvastatin on low-density lipoprotein subpopulations and comparison between indicators of plasma atherogenicity: a pilot study. Angiology. 2014;65:794-9

43. Banach M, Malodobra-Mazur M, Gluba A, et al. Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance. Curr Pharm Des. 2013;19:4904-12

44. Chrusciel P, Sahebkar A, Rembek-Wieliczko M, et al. Impact of statin therapy on plasma adiponectin concentrations: A systematic review and meta-analysis of 43 randomized controlled trial arms. Atherosclerosis. 2016;253:194-208

44. Thompson PD, Panza G, Zaleski A, et al. Statin-Associated Side Effects. J Am Coll Cardiol. 2016;67:2395-410

46. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J. 2013;166:597-603. Epub 2013/09/11

47. Esperion Therapeutics. A Study Of Pharmacokinetics, Pharmacodynamics And Safety Of Adding ETC-1002 To Atorvastatin 80 mg : Clinical trial.gov protocol 2016. Available from: https://clinicaltrials.gov/show/NCT02659397

48. Esperion Therapeutics. Esperion Therapeutics Announces Positive Top-Line Phase 2 Results for ETC-1002 in Patients With Hypercholesterolemia and Hypertension 2015. Available from: http://investor.esperion.com/releasedetail.cfm?ReleaseID=924113

49. Esperion Therapeutics. Esperion Therapeutics Provides Clinical Development and Regulatory Update for Bempedoic Acid 2016. Available from: https://globenewswire.com/news-release/2016/06/28/852085/0/en/Esperion-Therapeutics-Provides-Clinical-Development-and-Regulatory-Update-for-Bempedoic-Acid.html

ANNOTATED BIBLIOGRAPHY:

Stars	Reference	Author & Year	Comment

*	1	Shepherd (1995)	This study demonstrated the efficacy of pravastatin in primary prevention of CVD
*	2	SSSS Group (1994)	This study demonstrated the efficacy of simvastatin in secondary prevention of CVD
*	4	Baigent (2005)	Important meta-analysis demonstrating efficacy of lipid-lowering therapy with statins.
**	5	Cannon (2015)	Results of the IMPROVE-IT trial, demonstrating benefit of additional lipid lowering therapy in patients treated with statins.
**	14	Banach (2015)	This paper provides a clinically-useful definition of statin intolerance
**	20	Pinkosky (2016)	This paper presents detailed complete bempedoic acid mechanism of action
**	42	Thompson (2016)	An excellent overview of adverse effects of statin therapy

Table 1: Details of completed and ongoing phase 2 and trials with bempedoic acid.

Esperion reference	1002-003	1002-005	1002-006	1002-007	1002-008	1002-009	1002-014	1002-035	1002-040 CLEAR	1000-043
Completion date	10/2011	10/2012	05/2013	08/2013	11/2014	01/2015	07/2015	Expected 07/2016	Expected 04/2018	NA
Clinicaltrals.gov registration	NCT01262638	NCT01607294	NCT01751984	NCT01779453	NCT01941836	NCT02072161	NCT02178098	NCT02659397	NCT02666664	NA
Literature reference	[29, 30]	[31]	[32]	[34]	[36]	[35]	[33]	[46]	[37]	[48]
Status	Completed	Completed	Completed	Completed	Completed	Completed	Completed	Ongoing	Ongoing	Planned
Phase	2	2	2	2	2	2	2	2	3	3
Population	HC	HC + T2DM	HC+ statin intolerance	HC + Atorvastatin 10mg	HC + ezetimibe 10mg	HC + various statins	HC + hypertension	HC + atorvastatin 80mg	ACVD or FH	Intolerance of $\geq$ 2 statins.
Design	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial	Double blind Randomized controlled parallel group trial
Duration of trial	12 weeks	8 weeks	4 weeks	8 weeks	12 weeks	12 weeks	6 weeks	4 weeks	52 weeks	NA
Bempedoic acid daily dose	40mg 80mg 120mg	80mg	60mg	Titrated to 240mg + 10mg atorvastatin	120mg 180mg 120mg + EZE 180mg+ EZE	120mg + statin 180mg + statin	180mg	180mg + atorvastatin 80mg	180mg + statin	180mg + background therapy including lipid lowering drugs.
Control	Placebo	Placebo	Placebo	Placebo + 10mg atorvastatin	EZE	Placebo + statin	Placebo	Placebo + atorvastatin 80mg	Placebo + Statin	Placebo+ background therapy including lipid lowering drugs.
Participants	40mg: 45 80mg 44 120mg 44 Placebo 44	80mg 30 Placebo 30	60mg 37 Placebo 19	240mg 42 Placebo 16	120mg 99 180mg 100 120mg + EZE 26 180mg+ EZE 24 EZE 99	120mg + statin 43 180mg + statin 45 Placebo + statin 45	Total = 143	Estimated total = 60	Estimated total = 1950	Estimated total = 12,600
% males	40mg: 42 80mg 52 120mg 57 Placebo 70	80mg 57 Placebo 67	60mg 54 Placebo 42	NA	120mg 46 180mg 49 120mg + EZE 46 180mg+ EZE 46 EZE 48	120mg + statin 39 180mg + statin 31 Placebo + statin 51	NA	NA	NA	NA
Baseline BMI, kg/m^2	40mg: 27±4 80mg 29±4 120mg 28±3 Placebo 29±3	80mg 31±3 Placebo 29±3	60mg 30±4 Placebo 29±5	NA	120mg 31±6 180mg 31±5 120mg + EZE 30±5 180mg+ EZE 28±5 EZE 30±5	120mg + statin 30±6 180mg + statin 30±6 Placebo + statin 31±6	NA	NA	NA	NA
Baseline LDL-C, mg/dl	40mg: 163±25 80mg 170±26 120mg 165±23 Placebo 167±22	80mg 125±28 Placebo 128±29	60mg 176±37 Placebo 185±33	240mg 107±5 Placebo 104±7	120mg 164±28 180mg 166±24 120mg + EZE 162±26 180mg+ EZE 167±27 EZE 165±25	120mg + statin 134±20 180mg + statin 142±28 Placebo + statin 131±22	NA	NA	NA	NA
Baseline TC, mg/dl	40mg: 249±33 80mg 252±31 120mg 248±25 Placebo 250±26	80mg 206±36 Placebo 207±34	60mg 263±45 Placebo 276±43	NA	120mg 249±31 180mg 253±33 120mg + EZE 247±35 180mg+ EZE 246±32 EZE 248±32	120mg + statin 216±24 180mg + statin 229±29 Placebo + statin 212±24	NA	NA	NA	NA
Baseline HDL-C, mg/dl	40mg: 57±14 80mg 50±12 120mg 51±12 Placebo 49±11	80mg 44±10 Placebo 47±12	60mg 51±14 Placebo 58±18	NA	120mg 54±16 180mg 52±13 120mg + EZE 51±15 180mg+ EZE 52±16 EZE 49±12	120mg + statin 55±15 180mg + statin 55±14 Placebo + statin 54±14	NA	NA	NA	NA
Baseline triglycerides mg/dl	40mg: 148±66 80mg 158±68 120mg 159±74 Placebo 168±79	80mg 182‡ Placebo 152‡	60mg 200±172 Placebo 166±72	NA	120mg 136‡ 180mg 162‡ 120mg + EZE 161‡ 180mg+ EZE 151‡ EZE 163‡	120mg + statin 112‡ 180mg + statin 145‡ Placebo + statin 119‡	NA	NA	NA	NA

Baseline Lipoprotein (a), mg/dl	40mg: 32±35 80mg 29±28 120mg 24±25 Placebo 30±29	NA	NA	NA	NA	NA	NA	NA	NA	NA
Baseline hsCRP mg/l	40mg: 1.8‡ 80mg 1.9‡ 120mg 1.4‡ Placebo 1.8‡	80mg 2‡ Placebo 2‡	60mg 2.2‡ Placebo 1.6‡	NA	120mg 1.6‡ 180mg 2.5‡ 120mg + EZE 1.8‡ 180mg+ EZE 1.3‡ EZE 2.6‡	120mg + statin 1.8‡ 180mg + statin 1.8‡ Placebo + statin 1.8‡	NA	NA	NA	NA
Baseline glucose mg/dl	40mg: 95±10 80mg 97±7 120mg 94±9 Placebo 97±11	80mg 186±27 Placebo 198±32	NA	NA	NA	NA	NA	NA	NA	NA
Baseline SBP, mmHg	40mg: 119±11 80mg 121±9 120mg 119±9 Placebo 123±9	80mg 117±10 Placebo 120±13	NA	NA	120mg 126±11 180mg 125±12 120mg + EZE 126±12 180mg+ EZE 126±11 EZE 119±12	120mg + statin 128±11 180mg + statin 129±14 Placebo + statin 126±12	NA	NA	NA	NA
Baseline DBP, mmHg	40mg: 73±8 80mg 78±6 120mg 76±6 Placebo 78±7	80mg 77±6 Placebo 78±6	NA	NA	120mg 77±8 180mg 78±7 120mg + EZE 77±7 180mg+ EZE 76±9 EZE 78±7	120mg + statin 80±8 180mg + statin 78±9 Placebo + statin 78±7	NA	NA	NA	NA
% Change LDL-C !	40mg: -18±2**** 80mg -25±2**** 120mg -27±2**** Placebo -2±2****	80mg -43±3**** Placebo -4±3	60mg -32±2**** Placebo -3±3	240mg -22±3**** Placebo 0±5	120mg -28±1** 180mg -30±1**** 120mg + EZE -43±3**** 180mg+ EZE -48±3**** EZE -21±1	120mg + statin -17±4 180mg + statin -24±4** Placebo + statin -4±4****	NA	NA	NA	NA
% Change TC !	40mg: -12±2* 80mg -18±2* 120mg -17±2* Placebo -1±2	80mg -25±2**** Placebo -1±2	60mg -22±2**** Placebo -4±2	NA	120mg -19±1** 180mg -21±1**** 120mg + EZE -31±2**** 180mg+ EZE -34±2*** EZE -14±1	120mg + statin -13±3 180mg + statin -15±3** Placebo + statin -3±3**	NA	NA	NA	NA
% Change HDL !	40mg: 7±2 80mg 1±2 120mg 4±2 Placebo 2±2	80mg -1±2 **** Placebo -1±2	60mg -8±3 Placebo -2±4	NA	120mg 6±1**** 180mg 5±1**** 120mg + EZE 3±3* 180mg+ EZE 4±3** EZE 5±1	120mg + statin -6±3 180mg + statin -4±3 Placebo + statin -2±3	NA	NA	NA	NA
% Change hsCRP !	40mg: -21‡ 80mg -26‡ 120mg -20‡ Placebo -2‡	80mg -41** Placebo -11	60mg -42‡** Placebo 0‡	240mg -24 Placebo -9	120mg -30** 180mg -40** 120mg + EZE -38 180mg+ EZE -26* EZE -10	120mg + statin -22 180mg + statin -30 Placebo + statin 0	NA	NA	NA	NA

Values are reported as mean ± SD unless otherwise stated; !Least squares mean ± SEM ‡Median;*p<0.05 v control , **p<0.01 v control, ***p<0.001 v control, ****p<0.0001 v control

Abbreviations: CLEAR: **C**holesterol **L**owering via **E**TC-1002, an **A**CL-inhibiting **R**egimen; ACVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HC, hypercholesterolaemia; NA, not available; SBP, diastolic blood pressure; DBP, diastolic blood pressure; EZE = 10mg ezetimibe

Table 2: SWOT analysis relating to the potential use of bempedoic acid.

Strengths	• Orally bioavailable • Prodrug is activated only at site of action in liver, reducing potential for adverse effects • Demonstrated LDL-C and hsCRP lowering • No indication of adverse effects • Appears to be effective in diverse populations
Weaknesses	• No data yet available on hard clinical outcomes
Opportunities	• Combination therapy with statins or ezetimibe • Lipid-lowering in statin-intolerant patients • Potential for use in familial hypercholesterolaemia • Planned outcomes study
Threats	• Possibility that bempedoic acid will not show benefit in outcomes trials • Possibility of emergent idiosyncratic adverse effect in clinical trials

FIGURE LEGENDS:

Figure 1: Bempedoic acid (ETC-1002) is converted to ETC-1002-CoA by ACSVL1. ETC-1002-CoA inhibits ACL and therefore reduces downstream production of cholesterol and fatty acids by the mevalonate pathway.

***Abbreviations:** ACC, acetyl-coA carboxylase; ACL, Adenosine triphosphate-citrate lyase; HMG-CoA, Hydroxy-methyl-glutaryl-coenzyme A; HMGCR, Hydroxy-methyl-glutaryl-coenzyme A reductase.