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REVIEW ARTICLE

A Review of the Efficacy and Tolerability of Bempedoic Acid in the Treatment of Hypercholesterolemia

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Abstract
Despite the widespread use of statins and ezetimibe to decrease low-density lipoprotein cholesterol (LDL-C) levels and associated atherosclerotic cardiovascular disease (ASCVD), many patients do not achieve adequate LDL-C lowering as per the recommended American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines and demonstrate residual cardiovascular risk. The introduction of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors in 2015 was a promising addition to hypercholesterolemia therapies, but their cost and subcutaneous administration has limited their use, and therefore, new affordable and patient friendly treatment strategies are crucial to help reduce ASCVD risk. Bempedoic acid, a drug currently under investigation, is a small molecule that has been shown to upregulate LDL receptors, decrease LDL-C, and reduce atherosclerotic plaque formation in hypercholesterolemic patients. Furthermore, bempedoic acid is a prodrug that becomes activated by an enzyme expressed primarily in the liver, allowing it to avoid the potential myotoxicity associated with statin therapy. The purpose of this review is to summarize the major clinical studies evaluating bempedoic acid and describe its potential addition to currently approved lipid-lowering therapies.

1 Background

In the United States (US), 56 million adults over 40 years of age (48.6% of the population) are eligible for statin therapy due to low-density lipoprotein cholesterol (LDL-C) levels above 100 mg/dL [1]. LDL-C itself is a major risk factor for atherosclerotic cardiovascular disease (ASCVD), and irrespective of age, high LDL-C levels substantiality increase its risk. Currently, there are approximately eleven US Food and Drug Administration (FDA)-approved synthetic and biosynthetic therapies that are available to help reduce LDL-C, with the most utilized class of agents being the statins [2, 3]. Nevertheless, despite the substantial clinical and statistically significant LDL-C reduction by these agents, a large percentage of the population are not able to achieve a target LDL-C goal of less than 100 mg/dL, either because their LDL-C levels are too elevated or they are intolerant to statins and experience adverse effects, such as myalgia [1, 4, 5]. Thus, patients who cannot tolerate a statin-based treatment regimen present a challenge for lipid management and cardiovascular (CV) event risk reduction [6]. Additionally, patients who have familial hypercholesterolemia (FH) have greatly increased LDL-C levels that are unable to be lowered to the target LDL-C goal on statin monotherapy. This leaves a large unmet need for the development of additional therapies that reduce plasma LDL-C levels and ASCVD prevention.

The number of non-statin LDL-C–lowering therapies available at a clinician's disposal has expanded in recent years and includes proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, cholesterol-absorption inhibitors, bile acid resins, fibrates, and nicotinic agents. In addition to statins, two other LDL-C–lowering drug classes that have also demonstrated ASCVD reduction are cholesterol-absorption inhibitors (ezetimibe) and PCSK-9 inhibitors [evolocumab (Repatha) and alirocumab (Praluent)]. These

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Key Points

Bempedoic acid is a novel lipid-lowering therapy that inhibits adenosine triphosphate (ATP)-citrate lyases and has been shown to decrease low-density lipoprotein cholesterol (LDL-C) by approximately 15–24%.

Bempedoic acid is administered orally as a prodrug that only undergoes activation in the liver, allowing it to avoid the potential myotoxicity associated with statin therapy.

In January 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended approval of bempedoic acid and the fixed-dose combination of bempedoic acid/ezetimibe to treat adults with primary hypercholesterolemia and mixed dyslipidemia.

In February 2020 the US Food and Drug Administration (FDA) approved the use of bempedoic acid and the combination of bempedoic acid and ezetimibe as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL.

two classes are well-tolerated, with numerous clinical studies supporting their use over lipid-lowering therapies (LLTs) already established on the market; however, they still have their limitations. Cholesterol-absorption inhibitors only have modest LDL-C–lowering efficacy, in the range of 15–20%, while PCSK-9 inhibitors have more robust LDL-C–lowering effects (43–64%), have a high cost burden, and are only administered as a subcutaneous injection.

2 Cholesterol and Lipid-Lowering Therapies

Cholesterol is an essential structural component of cell membranes in the human body and serves as a precursor for the biosynthesis of numerous critical compounds such as steroid hormones, cell membrane, bile acid, and vitamin D. Cholesterol can be obtained exogenously through diet or synthesized within hepatocytes endogenously [7]. Disruption in cholesterol homeostasis due to hereditary factors or diet can lead to elevated plasma cholesterol levels that can produce fatty deposits in blood vessels, which, over time, can impede proper blood flow. This negative process can lead to the development of atherosclerosis and ASCVD.

Alterations in lipid and lipoprotein metabolism play an important role in the pathogenesis of CV disease (CVD), and addition of LLTs, such as statins, have significantly reduced CVD. Statins employ their mechanism of action by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, resulting in a compensatory increase in the expression of LDL receptors (LDL-Rs) on hepatocyte membranes and LDL-C catabolism. In addition to decreasing LDL-C by 30–50%, statins also reduce high-sensitivity C-reactive protein (hsCRP), improve endothelial function, reduce inflammation at the site of the coronary plaque, and inhibit platelet aggregation. The most common adverse events of statins are muscle related, ranging from myalgias to rare, but life-threatening, rhabdomyolysis, and are the number one reason for statin non-adherence and/or discontinuation [5, 6]. Statin-associated myopathy with significant elevation of serum creatine kinase (CK) is a rare but serious side effect of statins that affects up to one per 1000 people on statins. Statin-associated muscle symptoms, however, cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels. Preclinical studies show that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, thereby providing a potential link between statins and muscle symptoms [5]. Overall, statins have been shown to be efficacious in the lowering of LDL-C, and hold a strong recommendation in the American College of Cardiology (ACC)/American Heart Association (AHA) 2018 Guideline on the Management of Blood Cholesterol, for their use in patients with elevated LDL-C of > 100 mg/dL, as well as in the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines, for their use in the management of dyslipidemias—lipid modification to reduce CV risk. Nevertheless, in certain patients who are intolerant to statins or have FH, the use of statin monotherapy is not enough, and additional LLT is required to help further reduce LDL-C levels [1, 8].

Ezetimibe is a cholesterol-absorption inhibitor that lowers LDL-C by an average of 15–20% (Table 1) [9, 10]. It exerts its effects by inhibiting the absorption of cholesterol at the brush border of the small intestine through the sterol transporter, leading to a decrease in the delivery of cholesterol to the liver. This results in a reduction in hepatic cholesterol stores, which increases the clearance of cholesterol from the blood. In addition, IMPROVE-IT, a long-term safety and efficacy study that evaluated ezetimibe with simvastatin compared to simvastatin monotherapy in very high-risk acute coronary syndrome (ACS) subjects (within 10 days of an ACS event), demonstrated CV risk reduction with the addition of ezetimibe and supported the hypothesis that the lower the plasma LDL-C level, the lower the risk of CVD, myocardial infarction (MI), and stroke. The study also demonstrated that ezetimibe was not associated with myalgia, myopathy, rhabdomyolysis, and elevated hepatic transaminase, which are generally related to statin use [10, 11].

PCSK-9 inhibitors (evolocumab and alirocumab) are monoclonal antibodies that bind to PCSK-9, inhibiting its ability to bind to and degrade LDL-R on the hepatocyte surface. PCSK-9 inhibitors are powerful LDL-C–lowering agents with up to − 60% LDL-C reduction and are generally well-tolerated, with local injection site reactions as the only main adverse event. In addition, long-term outcome studies with evolocumab and alirocumab were associated with reductions in LDL-C from baseline of 56–59%, with no increase in overall rates of adverse events and no neutralizing antibodies (Table 1) [19, 20]. Along with alirocumab and evolocumab, a third agent, inclisiran sodium, which inhibits the production of PCSK-9, is being studied in phase 3 trials. Inclisiran sodium is a silencing RNA that inhibits PCSK-9 protein synthesis and has an advantage over alirocumab and evolocumab due to its ability to be administered as a subcutaneous injection every 6 months, with long-lasting and durable LDL-C reduction [21, 22].

Other LLTs currently available include bile acid sequestrants, fibrates, and nicotinic acid agents, none of which compare to the efficacy of statins, cholesterol-absorption inhibitors, and PCSK-9 inhibitors (Table 1). Bile acid sequestrants, such as cholestyramine, colestipol, and colesevelam, bind bile acids in the intestine to form an insoluble complex that is eliminated in the feces, forcing the liver to create more bile acid. This increases oxidation of cholesterol to bile acid and lowers LDL-C levels by about 15–30%. This process results in gastrointestinal adverse events, such as bloating, diarrhea, constipation, and flatulence [9]. Fenofibric acid agents (fibrates) are an agonist for the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha), which downregulates apoprotein C-III (an inhibitor of lipoprotein lipase) and upregulates the synthesis of apolipoprotein A-I (ApoA-I), fatty acid transport protein, and lipoprotein lipase. This results in an increase in very low-density lipoprotein (VLDL) catabolism, fatty acid oxidation, and elimination of triglyceride (TG)-rich particles. Due to the decrease in VLDL levels, total plasma TGs are reduced. Fibrates, such as gemfibrozil and fenofibrate, mainly reduce TGs (20–35%), but also reduce LDL-C

Table 1 Approved LLTs and their effects on lipid levels compared with bempedoic acid [12–18]

Drug class	Agents	Effects on lipids	Side effects
HMG-CoA reductase inhibitors	Atorvastatin (Lipitor®) Lovastatin (Mevacor®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®) Fluvastatin (Lescol®) Pitavastatin (Livalo®, Zypitamag®) Advicor® (lovastatin + niacin) Vytorin™ (simvastatin + ezetimibe)	LDL-C: ↓ 20–50% TG: ↓ 10–20% HDL: ↑ 5–10%	Myalgia Myopathy Rhabdomyolysis Elevated hepatic transaminase
PCSK-9 inhibitors	Alirocumab (Praluent®) Evolocumab (Repatha®)	LDL-C: ↓ 50–60% TG: ↓ 1–17% HDL: ↑ 3–8%	Local injection site reaction
Cholesterol-absorption inhibitors	Ezetimibe (Zetia®)	LDL-C: ↓ 13–20% TG: ↓ 2% HDL: ↑ 1%	Diarrhea
Nicotinic acid	Niacin (Niacin-50®, Niacor®, Niaspan®, Slo-Niacin®)	LDL-C: ↓ 5–10% TG: ↓ 20–35% HDL: ↑ 15–30%	Flushing Rash Diarrhea Hyperuricemia Hyperglycemia
Fibric acids	Fenofibrate (Antara®, Lipofen®, Tricor®) Fenofibric acid (Trilipix®, Fibricor®) Gemfibrozil (Lopid®)	LDL-C: ↓ 20–30% TG: ↓ 20–40% HDL: ↑ 9–15%	Gastrointestinal upset Dyspepsia Rash Abdominal pain Elevated hepatic transaminase
Bile acid sequestrants	Colesevelam (Welchol®) Cholestyramine (Prevlite®, Questran®, Questran Light®) Colestipol (Colestid®)	LDL-C: ↓ 15–30% TG: ↑ 5–10% HDL-C: ↑ 3–5%	Constipation Nausea Bloating
ATP citrate lyase (ACL) inhibitor	Bempedoic acid (Nexletol™) Bempedoic acid + ezetimibe (Nexlizet™)	LDL-C: ↓ 28% TG: ↓ 3% HDL: ↑ 6%	No significant side effects Occurrence of myalgias similar to that with placebo

ATP adenosine triphosphate, *HDL* high-density lipoprotein, *HMG-CoA* 3-hydroxy-3-methyl-glutaryl-CoA, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *PCSK-9* proprotein convertase subtilisin/kexin type 9, *TG* triglyceride

by 20–25% and increase high-density lipoprotein (HDL) cholesterol (HDL-C) by 6–18% [23]. Lastly, nicotinic acid agents (niacin) inhibits a hormone-sensitive lipase in adipose tissue, which reduces the breakdown of TGs to free fatty acids and the transport of free fatty acids to the liver. The reduction in transport of free fatty acids from fat to the liver decreases hepatic TG synthesis, inhibiting VLDL secretion from hepatocytes, which in turn decreases the production of LDL-C. The catabolic rate for HDL is decreased as well. Niacin can lower LDL-C up to 10–25% and TGs by approximately 20–30%, but is minimal and only indicated, as per the AHA/ACC 2018 Guideline on the Management of Blood Cholesterol, for patients with extremely high TGs (> 500 mg/dL) [1].

3 Bempedoic Acid Mechanism of Action and Pharmacology

Bempedoic acid (ETC-1002 or 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is a novel, non-statin, once-daily, oral drug being developed for the treatment of primary hyperlipidemia in combination with other LLTs in patients who need additional lipid lowering. In comparison to already approved LLTs, bempedoic acid not only has the potential to improve lipid levels, it affects these levels through a different mechanism of action (Fig. 1). Similar to statins, the predominant biochemical mechanism of action of bempedoic acid is through increased LDL-R activity and consequent reduction in the plasma concentration of LDL-C. Bempedoic acid (ETC-1002) is a prodrug that requires conversion by acyl-CoA synthease-1 (ACSVL1) to its active moiety, ETC-1002-coenzyme A (ETC-1002-CoA). The active form of bempedoic acid (ETC-1002-CoA) acts as a competitive inhibitor of the enzyme adenosine triphosphate (ATP)-citrate lyase (ACL) and reduces the production of cytosolic acetyl-coenzyme A (acetyl-CoA), the final substrate for both fatty acid and sterol synthesis, located upstream of HMG-CoA in the cholesterol biosynthesis pathway (Fig. 1). The active form of bempedoic acid (ETC-1002-CoA) also increases 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation, which results in inhibitory phosphorylation of acetyl-CoA carboxylase (ACC) and HMG-CoA reductase. In summary, bempedoic acid's suppression of cholesterol synthesis through ACL inhibition and activation of AMPK in turn upregulates LDL-R activity, causing a reduction in circulating LDL-C [6, 24].

A recent article by Ference et al. [25] evaluated the link between the genetic inhibition of ACL and deleterious outcomes and whether it has the same effect, per unit decrease in the LDL-C level, as the genetic inhibition of HMG-CoA reductase. This study found that variants in ACL and HMG-CoA reductase were associated with similar changes in the concentration and lipid composition of plasma lipoproteins, and both agents had a nearly identical effect on the risk of CV events. Therefore, the results confirmed the mechanism by which ACL inhibition lowers plasma LDL-C levels and validated ACL inhibition as a genetic target [25].

The primary benefit of bempedoic acid over statins is that the enzyme ACSVL1, required for activation, is not present in the skeletal muscle. Therefore, bempedoic acid is not converted to its active form within skeletal muscle, limiting the possibility of a common adverse effect of statins, myalgia [24]. Another major benefit of bempedoic acid is that this compound can reduce hsCRP, which is commonly seen with statins, but not with PCSK-9 inhibitors [26].

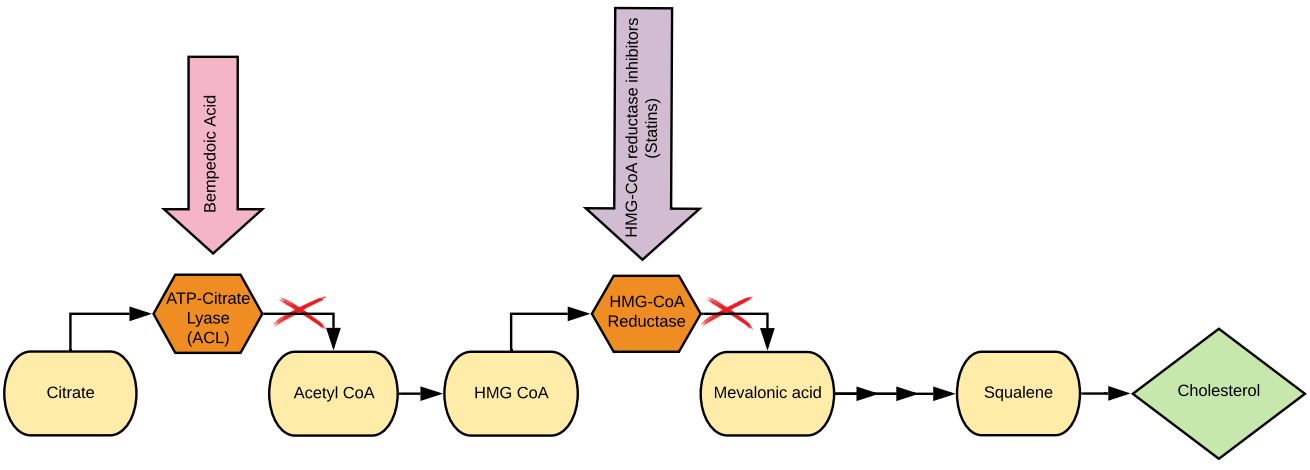

Fig. 1 Mechanism of action: bempedoic acid and HMG-CoA reductase inhibitors. *ATP* adenosine triphosphate, *HMG-CoA* 3-hydroxy-3-methylglutaryl-CoA

3.1 Bempedoic Acid Preclinical Pharmacology and Phase 1 Clinical Studies

Preclinical models with bempedoic acid demonstrated that bempedoic acid achieves its primary mechanism of action through a direct inhibition of hepatic ACL and increased AMPK activation [4, 27]. A preclinical in vivo study done by Pinkosky et al. [4] tested the efficacy and safety of bempedoic acid in male hamsters with induced hyperlipidemia. A vehicle consisting of 0.5% carboxymethyl cellulose (CMC) and 0.025% Tween-20 or bempedoic acid 30 mg/kg/day plus vehicle for 3 weeks was administered through an oral gauge once daily. In hamsters treated with bempedoic acid, body weight was reduced by − 14.4% ($p < 0.01$), plasma TG by − 41% ($p < 0.05$), total cholesterol (TC) by − 41% ($p < 0.05$), and LDL-C by − 64% ($p < 0.05$). A parallel in vivo study was also conducted by Pinkosky et al. [27]; it tested the efficacy of bempedoic acid in male mice that were fed a high-fat diet. At week 20, the mice were randomized to either receive CMC and Tween-20 or 30/mg/kg/day bempedoic acid through an oral gauge. In mice treated with bempedoic acid, a 9% reduction in body weight ($p < 0.05$) was observed in addition to a 13% reduction in plasma glucose levels ($p < 0.05$). The robust effects of bempedoic acid on lipid parameters along with improved glucose homeostasis may suggest that there may be other possible beneficial effects of bempedoic acid in addition to its lipid-lowering capabilities.

A staged 2-week and 4-week, phase 1b [28], multiple-ascending dose study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of bempedoic acid in dosages up to 120 mg once daily in 53 healthy subjects aged 18–55 years with a baseline LDL-C of 100–160 mg/dL. In the study [29], 39 subjects received bempedoic acid (20 mg, 60 mg, 100 mg, or 120 mg) and 14 received placebo, of which 21 received treatment for 28 days (15 on bempedoic acid 120 mg and six on placebo) [28]. A maximal LDL-C reduction of − 17% was found with bempedoic acid 100 mg after 2 weeks of treatment and − 16% after 4 weeks of treatment with bempedoic acid 120 mg. The study demonstrated that the PK of bempedoic acid were well characterized, supporting once-daily dosing, and the drug was safe, well-tolerated, and not associated with dose-limiting adverse effects [6, 29].

A 2-week, phase 1b, multiple-ascending dose study was completed [30], which evaluated the safety, tolerability, and PK of bempedoic acid in dosages greater than 120 mg once daily. The study examined 18 subjects that received bempedoic acid (140 mg, 180 mg, or 220 mg daily) and six subjects that received placebo for 14 days. The study demonstrated that LDL-C levels were reduced by up to − 36% in subjects receiving bempedoic acid 220 mg/day compared to a 4% increase in LDL-C in subjects receiving placebo ($p < 0.0001$). In addition, no serious adverse events were noted with subjects in the bempedoic acid group over the 2-week period. Overall, bempedoic acid was observed to be safe and well-tolerated, with no dose-limiting adverse effects [6, 31].

3.2 Bempedoic Acid Phase 2 Clinical Studies

3.2.1 Non-diabetic Patients Compared with Placebo

A phase 2a study completed by Ballantyne et al. [32] evaluated the safety and efficacy of bempedoic acid in non-diabetic subjects with hypercholesterolemia with or without elevated TG levels. A total of 177 subjects aged 18–80 years with an LDL-C of 130–220 mg/dL (after a 6-week washout of all background LLTs) were randomized (1:1:1:1) to bempedoic acid 40, 80, or 120 mg orally once daily or matching placebo for 12 weeks. Within the overall study population, the least squared (LS) mean percentage changes in LDL-C from baseline to week 12 were − 17.9%, − 25.0%, and − 26.6% in the bempedoic acid 40-, 80-, and 120-mg treatment groups, respectively, compared with − 2.1% in the placebo group ($p < 0.0001$), demonstrating a dose-dependent reduction in LDL-C with bempedoic acid [32]. The results of the study demonstrated that bempedoic acid reached its maximum LDL-C reduction after 2 weeks of treatment, which was maintained throughout the study, and baseline TG levels did not influence its efficacy. With respect to secondary endpoints, bempedoic acid statistically reduced non-HDL-C (− 17.4 mg/dL, − 22.7 mg/dL, − 23.0 mg/dL), apolipoprotein B-100 (apoB) (− 14.6 mg/dL, − 18.4 mg/dL, − 22.1 mg/dL), and LDL particle number (− 14.8 nmol/L, − 16.3 nmol/L, − 20.7 nmol/L) in a dose-dependent manner at all dose levels (40 mg, 80 mg, and 120 mg, respectively; $p < 0.0001$ for all vs. placebo). Bempedoic acid also decreased TGs and increased HDL-C, but these changes did not reach statistical significance and were not dose related. In a post-hoc exploratory analysis, bempedoic acid demonstrated additional CV benefits, such as a trend toward a decrease in diastolic blood pressure (DBP) of 2.5–6 mmHg in a small subgroup of subjects with mildly elevated baseline DBP (greater than 80 mmHg). Bempedoic acid was generally safe and well-tolerated, with headaches being the most common adverse event. The safety profile was similar to placebo, with 15% ($n = 26$) discontinuation due to side effects. Myalgia was reported in 4%, 5%, and 7% of subjects in the 40-, 80-, and 120-mg treatment groups, respectively, and in none of the placebo-treated subjects. Seven patients experienced myalgia, one of whom was receiving bempedoic acid 80 mg and was withdrawn from the trial due to this adverse event, whereas all other subjects completed 12 weeks of treatment [29, 32].

A phase 2a exploratory clinical safety study evaluated bempedoic acid 180 mg in patients with LDL-C between 100 and 220 mg/dL and mean 24-h ambulatory systolic blood pressure (SBP) ≥ 130 mmHg or DBP ≥ 80 mmHg. In this study, 143 patients were washed out of any LLTs and blood pressure therapies for up to 6 weeks prior to therapy initiation and were randomized 1:1 to receive bempedoic acid 180 mg or placebo daily. The primary endpoint of this clinical study was the percentage change in LDL-C between the two groups. Patients receiving bempedoic acid achieved a − 21% LDL-C lowering at 6 weeks compared to a 3% increase in the placebo group ($p < 0.0001$). A − 25% reduction in hsCRP levels was also observed in patients treated with bempedoic acid versus the placebo group, which had a 20% increase in hsCRP ($p < 0.0001$), with a neutral effect on blood pressure in the bempedoic acid group. Overall, in this study, bempedoic acid was well-tolerated, with no occurrence of serious adverse events [6, 33].

In a phase 2a study conducted by Thompson et al. at five sites in the US, the efficacy and safety of bempedoic acid in 56 subjects with hypercholesterolemia and a history of statin intolerance were evaluated [34]. This study examined bempedoic acid versus placebo in subjects 18–80 years of age with hypercholesterolemia (defined as LDL-C 100–220 mg/dL if on LLT at baseline or LDL-C 115–270 mg/dL if not on LLT at baseline) and a history of intolerance, with myalgia, muscle cramps, muscle aches, or muscle weakness, to one or more statins [29]. Prior to initiating study treatment, eligible subjects underwent a washout of any LLTs for at least 4 weeks, which included 2 weeks of a placebo run-in period that excluded subjects who reported muscle-related or other clinically significant adverse events. Subjects were randomized (2:1) to bempedoic acid (60 mg once daily for 2 weeks and titrated at 2-week intervals to 120, 180, and 240 mg daily) or placebo. After 8 weeks of treatment, bempedoic acid met its primary endpoint and reduced LDL-C by − 32.0% from baseline compared to − 3.3% with placebo, with a difference in the percentage reduction of − 28.7% ($p < 0.0001$). The reduction from baseline in LDL-C with bempedoic acid was 18.0% greater at week 2 than with placebo, and this difference increased to 28.5% and 30.0% at weeks 4 and 8, respectively ($p < 0.0001$) (Thompson et al. 2015). Furthermore, 62% of the subjects in the bempedoic acid group who were not at their LDL-C goal at baseline achieved their LDL-C goal at week 8 compared to no subjects in the placebo group ($p < 0.0001$). Secondary endpoints were the percentage change in non-HDL-C, TC, HDL-C, TGs, apoB, and hsCRP. Bempedoic acid compared to placebo statistically reduced non–HDL-C by − 20.9% ($p < 0.0001$), TC by − 18.4% ($p < 0.0001$), and apoB by − 15.3% ($p = 0.0019$) from baseline to 8 weeks. However, there was no statistically significant difference in bempedoic acid's effects on HDL-C, TGs, or ApoA-1. A reduction trend was found for non-HDL-C, with bempedoic acid resulting in a − 14% reduction at week 2, which decreased further to − 25% after 8 weeks of treatment, and though bempedoic acid was superior to placebo in the hsCRP reduction (− 42%), there was no differences seen for lipoprotein(a) and free fatty acids. The safety profile of bempedoic acid was very good in this study, and none of the patients in the bempedoic acid arm discontinued the drug because of muscle-related adverse events [34].

3.2.2 Non-diabetic Patients Compared with Other LDL-C–Lowering Therapy

A phase 2a study evaluated the safety and PK interaction of bempedoic acid and atorvastatin 10 mg. 58 subjects with hypercholesterolemia with or without background statin therapy were placed on atorvastatin 10 mg once daily for 4 weeks after washing out all LLTs at screening [35] and then randomized (3:1) to add bempedoic acid or placebo for 8 weeks [29]. Subjects randomized to bempedoic acid were initiated on 60 mg once daily, with forced titrations every 2 weeks to 120 mg, 180 mg, and 240 mg once daily. The primary outcome measures were the PK profile of bempedoic acid and atorvastatin (e.g., plasma concentration of atorvastatin and its metabolites, and adverse events), and the study demonstrated a weak PK interaction with bempedoic acid and atorvastatin, but the combination was well-tolerated and did not result in any serious adverse events [30]. A secondary endpoint, LDL-C lowering from baseline to 8 weeks, demonstrated that bempedoic acid reduced LDL-C by an average of − 22% compared with 0% in the placebo group ($p < 0.0001$). However, no significant changes in HDL-C or TG levels were observed. Two patients in the bempedoic acid plus atorvastatin group withdrew from the study due to adverse events, one of whom had elevated liver enzymes that resolved when bempedoic acid and atorvastatin were discontinued, and the other subject's adverse event was unrelated to treatment [36].

A phase 2b study conducted by Thompson et al. [18] was a 12-week study that evaluated the efficacy and safety of bempedoic acid monotherapy and bempedoic acid in combination with ezetimibe 10 mg compared to ezetimibe 10 mg alone. The study examined subjects with hypercholesterolemia (LDL-C 130–220 mg/dL, with fasting TG levels of ≤ 400 mg/dL) with ($n = 177$) or without ($n = 171$) a history of statin intolerance (due to muscle-related symptoms) to two or more statins. Prior to randomization, eligible subjects underwent a 5-week washout period of all background LLTs and dietary supplements, and these therapies were not re-initiated throughout the study. Subjects were then randomized to a 4:4:4:1:1 ratio to bempedoic acid 120 mg, bempedoic acid 180 mg, bempedoic acid 120 mg plus ezetimibe 10 mg, bempedoic acid 180 mg plus ezetimibe 10

mg, or ezetimibe 10 mg alone [18]. The results for this study showed that bempedoic acid 120 mg and 180 mg monotherapy lowered LDL-C by −27.5% ($p < 0.01$) and −30.1% ($p < 0.0001$), compared to ezetimibe monotherapy, which was shown to be not significant, with an LDL-C lowering of −21.2%. Additionally, the combination of bempedoic acid 120 mg plus ezetimibe and bempedoic acid 180 mg plus ezetimibe demonstrated the greatest LDL-C reductions of −43% and −48%, ($p < 0.0001$ for both). This significant incremental decrease in LDL-C with combination therapy may be due to the complementary mechanisms of action of these two drug classes. In relation to safety endpoints, the occurrence of adverse events was similar between the bempedoic acid group and the ezetimibe monotherapy group. Muscle-related adverse events were comparable between the combination treatment groups and were fewer in the bempedoic acid monotherapy group (120 mg, $n = 3$ and 180 mg, $n = 1$) than in the ezetimibe group (10 mg, $n = 6$) [18]. Overall, this study demonstrated that bempedoic acid plus ezetimibe had similar LDL-C lowering to that of ezetimibe statin combination therapies that are currently found in the market.

Another phase 2b, multicenter study, conducted by Ballantyne et al. [37], evaluated bempedoic acid as an add-on therapy in subjects with persistently elevated LDL-C despite statin therapy. This study enrolled 134 subjects with hypercholesterolemia, defined as LDL-C levels from 115 to 220 mg/dL and TG ≤ 400 mg/dL, who were on a stable background statin therapy with atorvastatin ≤ 20 mg, simvastatin ≤ 20 mg, rosuvastatin ≤ 10 mg, or pravastatin ≤ 40 mg for at least 3 months before screening (Ballantyne et al. 2016). Subjects underwent a 6-week screening and washout phase and were then randomized (1:1:1) to bempedoic acid 120 mg or 180 mg or matching placebo once daily for 12 weeks in addition to background statin therapy. Subjects were stratified based on their history of statin intolerance, defined as discontinuation of one or more statins due to muscle-related symptoms. The primary efficacy endpoint was percentage change in LDL-C levels from baseline to week 12 in subjects treated with bempedoic acid versus those treated with placebo. At the end of week 12, treatment with bempedoic acid was statistically significant for LDL-C reductions from baseline for 120 mg (−17.3%, $p < 0.01$) and for 180 mg (−24.3%, $p < 0.0001$) compared to placebo, which was −4.2%. These effects were stable by week 2 and remained significantly lower than placebo through week 12 [37]. A non-significant reduction of hsCRP was also found in the bempedoic acid 120-mg group, with a median reduction of −22% ($p = 0.26$) and −30% in the 180-mg group ($p = 0.08$), with no significant effect on TG levels (−4.8 and −9.1, $p < 0.01$ for both). However, a significant reduction was noted in subjects in the bempedoic acid 120-mg and 180-mg groups for apoB (−15%, $p < 0.001$ and −17.2, $p < 0.01$), non–HDL-C (−14.3% and −16.6%, $p < 0.01$ for both), and TC (−12.8% and −15.3%, $p < 0.01$ for both) compared to placebo (−5.5%, −1.8%, −3.2%). Muscle-related adverse events were less frequent with bempedoic acid (2–5%) compared to placebo (13%). None discontinued due to muscle-related adverse events, and the percentage of patients discontinuing because of adverse events was similar between all three groups [37].

3.2.3 Diabetic Patients

In a phase 2a trial, Gutierrez et al. [29, 38] evaluated the lipid-altering effects of bempedoic acid in patients with type 2 diabetes mellitus (T2DM). 60 subjects washed out of all anti-diabetic agents and LLTs were randomized (1:1) to receive bempedoic acid (80 mg once daily for 2 weeks followed by 120 mg once daily for 2 weeks) or placebo (for 4 weeks). After 4 weeks, the primary endpoint (change from baseline in LDL-C) was met, and subjects treated with bempedoic acid experienced lowering of LDL-C levels by −43%, compared with a reduction of −4% with placebo at day 28 ($p < 0.0001$). The study also revealed that non–HDL-C levels were also significantly lowered by bempedoic acid compared with placebo [−32% vs. 1% ($p < 0.0001$)], but HDL-C and TG levels were not affected. A similar analysis was performed at day 15, which assessed the effect of the 80-mg dosage. Furthermore, of the 80% of subjects who were not at their LDL-C goal of < 100 mg/dL at baseline, 88% who received bempedoic acid achieved their goal compared to those on placebo (4%; $p < 0.0001$), which is a significant difference [29]. When looking at potential pleiotropic effects of bempedoic acid, hsCRP was reduced by −41% in subjects taking bempedoic acid 120 mg compared with those on placebo (−11%; $p = 0.001$), which was also found with statins, and no worsening of blood glucose was identified with treatment. In fact, in subjects taking bempedoic acid, a trend was seen towards improved glucose control and insulin resistance. Lastly, a post-hoc analysis with nine subjects who had mildly elevated DBP (> 80 mmHg) at baseline demonstrated that those taking bempedoic acid obtained a lowering of DBP of −7.8 mmHg compared to −0.4 mmHg with those on placebo ($p = 0.047$). Regarding the adverse effects of the medication in the study, headache was the most common (six in the bempedoic acid arm and three in the placebo arm), but no subjects reported myalgia or experienced substantial elevations in lab parameters [6]. Bempedoic acid treatment did not result in a worsening of glycemic control, and a nonsignificant reduction of all prespecified glycemic markers was observed at day 29 compared with placebo. These prespecified glycemic markers included fasting plasma glucose concentrations (−8.5 mg/dL), 15-h weighted mean plasma glucose (−14.3 mg/dL), and morning postprandial plasma glucose area under

the concentration–time curve (AUC) from time 0 to 4 h after the glucose meal tolerance test standardized meal (− 79.2 mg/dL). A 24-h continuous glucose monitoring assessment showed a nonsignificant trend of improved glycemic control, particularly associated with reduced postprandial meal peaks, compared with placebo. A post-hoc analysis of a subgroup of patients with mild elevation in DBP at baseline (> 80 mmHg) showed that treatment with bempedoic acid decreased DBP compared with placebo on day 28 (− 7.3 mmHg; $p = 0.0474$). In a similar post-hoc analysis of patients with mild elevation in SBP at baseline (> 120 mmHg), treatment with bempedoic acid trended toward a decrease in SBP compared with placebo on day 28 (− 2.4 mmHg; $p = 0.3271$) [38].

3.3 Bempedoic Acid Phase 3 Clinical Studies

Bempedoic acid was studied in four major phase 3 clinical outcome studies, Harmony, Tranquility, Serenity, and Wisdom, as part of the Cholesterol Lowering through Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) program (Table 2).

The CLEAR Harmony study assessed the long-term safety and efficacy of bempedoic acid versus placebo in subjects who had a history of ASCVD, heterozygous familial hypercholesterolemia (HeFH), or both and LDL-C levels ≥ 70 mg/dL who were receiving maximally tolerated statin therapy alone or in combination with additional LLTs [39]. In the study, 2230 subjects were randomized (2:1 ratio) to receive bempedoic acid 180 mg orally once daily or matching placebo for 52 weeks. The primary endpoint of safety with bempedoic acid was acceptable, with the most frequent key adverse events being myalgia (6.0% vs. 6.1%) and muscle spasm (4.2% vs. 2.7%) in the bempedoic acid arm versus placebo. Although the occurrence of adverse events did not differ substantially between the bempedoic acid and placebo groups (78.5% vs. 78.7%), the incidence of adverse events leading to discontinuation of the regimen was higher in the bempedoic acid group compared to placebo (10.9% vs. 7.1%), as was the incidence of gout (1.2% vs. 0.3%). Nevertheless, the percentages of patients who discontinued treatment due to muscle-related adverse events were low in the two groups (2.1% in the bempedoic acid group and 1.9% in the placebo group) [39]. The efficacy of bempedoic acid was evaluated as a secondary endpoint, where the percentage reduction of plasma LDL-C from baseline to week 12 was measured. Bempedoic acid demonstrated statistical significance through a mean reduction in LDL-C levels of − 19.2 mg/dL at week 12, with a − 18.1% decrease in LDL-C levels from baseline compared to − 16.1% with placebo ($p < 0.001$). This lipid-lowering effect was maintained at week 24, with an LDL-C lowering of − 16.1% from baseline, and was seen through the 52 weeks of treatment even with the varying intensity of other LLT [39]. Furthermore, in addition to plasma LDL-C reduction, subjects in the bempedoic acid group compared to placebo showed a significant decrease in non–HDL-C, TC, apoB, and hsCRP (− 13.3%, 11.1%, − 11.9%, and − 21.5%, respectively, $p < 0.001$ for all) at week 12 [39].

The CLEAR Tranquility study was a year-long study that evaluated the efficacy and safety of bempedoic acid plus ezetimibe compared to placebo and ezetimibe in subjects with fasting LDL-C ≥ 100 mg/dL and a history of statin intolerance (receiving low-dose statin or no statin therapy) in addition to other background LLT [40]. In the study, 269 eligible subjects were randomized in a 2:1 ratio to bempedoic acid 180 mg daily with ezetimibe 10 mg daily or placebo with ezetimibe 10 mg daily. Concomitant LLTs, in addition to ezetimibe, were used by 47.5% of subjects in the bempedoic acid group (of which 32.6% were receiving low-dose concomitant statin therapy) and 39.1% of subjects in the placebo group (of which 27.6% were receiving a statin). The combination of bempedoic acid and ezetimibe in addition to background LLT met its primary endpoint by demonstrating a mean change in LDL-C of − 28.5% ($p < 0.001$) at week 12 from baseline. In addition, at week 12, subjects in the bempedoic acid group had a reduction in mean LDL-C to 96.2 mg/dL from a baseline LDL-C of 129.8 mg/dL, whereas in the placebo group, subjects had a mean increase in LDL-C to 128.8 mg/dL from a baseline LDL-C level of 123.0 mg/dL. [40]. The secondary endpoints, which included changes in other atherogenic parameters, significantly favored the bempedoic acid group compared to placebo, with an LS mean change in non-HDL-C of − 18.4% vs. 5.2% ($p < 0.001$), TC of − 15.1% vs. 2.9% ($p = 0.001$), apoB of − 14.6% vs. 4.7% ($p = 0.001$), and hsCRP of − 32.5% vs. 2.1% ($p < 0.001$) at week 12 from baseline. However, a decrease in HDL-C levels in the bempedoic acid and placebo groups was observed (− 7.3% vs. − 1.4%, $p = 0.002$), with a slight median change in TG levels (−1.4% vs. 7.8%). Additionally, the LDL-C reduction with bempedoic acid was greater in subjects who were on non-statin or no background therapy (− 34.7%; $p < 0.001$) compared with those who were on a low-dose or very low-dose of statin therapy at baseline (− 20.5%; $p = 0.003$) [40]. Adverse events were reported by 48.6% and 44.8% of patients in the bempedoic acid and placebo treatment groups, and muscle-related adverse events occurred equally across both treatment groups (3.3% and 3.4%). Rates of discontinuation due to an adverse event were similar in the bempedoic acid and placebo groups (6.1% vs. 5.7%). Three subjects discontinued study treatment due to muscle-related adverse events, from which, two were from the bempedoic acid group (one subject discontinued due to muscle spasms and one due to pain in extremity), whereas, myalgia was experienced by one patient in the placebo group who discontinued study treatment. Nevertheless, both patients in

Table 2 Summary of the CLEAR trials [39–42]

CLEAR trial	Patient population	Comparator agent	LDL-C reduction from baseline
Harmony	ASCVD and/or HeFH	Bempedoic acid 180 mg vs. placebo	− 19.2% bempedoic acid vs. + 1.6% placebo ($p < 0.001$) at week 12
	Receiving maximally tolerated statin therapy with or without additional LLT		− 16.1% bempedoic acid vs. + 1.2% placebo ($p < 0.001$) at week 24
	Fasting LDL-C ≥70 mg/dL		− 12.6% bempedoic acid vs. + 1% placebo ($p < 0.001$) at week 52
Tranquility	History of statin intolerance with no more than low-dose statin therapy	Bempedoic acid 180 mg plus ezetimibe 10 mg vs. placebo plus ezetimibe 10 mg	− 28.5% bempedoic acid plus ezetimibe vs. + 5.0% placebo plus ezetimibe ($p < 0.001$) at week 12
	Fasting LDL-C ≥ 100 mg/dL		
Serenity	History of statin intolerance to at least two statins	Bempedoic acid 180 mg vs. placebo	− 23.6% bempedoic acid vs. − 1.3% placebo ($p < 0.001$) at week 12
	Fasting LDL ≥ 130 mg/dL for primary prevention or fasting LDL ≥ 100 mg/dL for HeFH and/or secondary prevention for ASCVD		− 22.1% bempedoic acid vs. − 2.3% placebo ($p < 0.001$) at week 24
Wisdom	ASCVD and/or HeFH	Bempedoic acid 180 mg vs. placebo	− 15.1% bempedoic acid vs. + 2.4% placebo ($p < 0.001$) at week 12
	Receiving maximally tolerated statin dose		− 12.1% bempedoic acid vs. + 2.7% placebo ($p < 0.001$) at week 24
	Fasting LDL-C ≥ 100 mg/dL		

ASCVD atherosclerotic cardiovascular disease, *ACL* adenosine triphosphate (ATP)-citrate lyase, *CLEAR* Cholesterol Lowering through Bempedoic Acid, an ACL-Inhibiting Regimen, *HeFH* heterozygous familial hypercholesterolemia, *LDL* low-density lipoprotein, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy

the bempedoic acid treatment group who withdrew due to muscle-related adverse events were receiving concomitant statin therapy. There was a slight increase in mean uric acid concentrations, 7.7% in the bempedoic acid group and 2.3% in the placebo group, with no new-onset or worsening of gout reported [40]. Overall, the CLEAR Tranquility study successfully proved the efficacy and safety of bempedoic acid 180 mg when compared to background therapy that included ezetimibe 10 mg.

The CLEAR Serenity study evaluated the efficacy and safety of bempedoic acid in statin intolerant subjects (unable to tolerate two or more statins) with an LDL-C ≥ 130 mg/dL for primary prevention and an LDL-C ≥ 100 mg/dL for subjects with HeFH for secondary prevention of coronary artery disease (CAD), symptomatic peripheral arterial disease (PAD), and/or cerebrovascular atherosclerotic disease. A total of 354 subjects were randomized 2:1 to receive bempedoic acid 180 mg or placebo once daily for 24 weeks [41]. The primary endpoint of mean percentage change in LDL-C levels from baseline to week 12 was statistically significant for bempedoic acid over placebo (− 23.6% vs. − 1.3%, $p < 0.001$). Significant reductions in secondary outcomes for various lipid markers were also observed in the bempedoic acid group compared to placebo at week 12 from baseline for non-HDL-C (− 19% vs. − 0.4%, $p < 0.001$), TC (− 16.1% vs. − 0.6%, $p < 0.001$), apoB (− 15.0% vs. − 0.2%, $p < 0.001$), and hsCRP (− 25.4% vs. 2.7%, $p < 0.001$). In addition, in both groups, changes in TGs were minimal and effects on HDL-C were negligible. Additionally, a post-hoc analysis that was conducted to analyze the percentage change in LDL-C from baseline resultant from background LLTs. Greater reductions in LDL-C with bempedoic acid versus placebo was demonstrated in subjects receiving no background LLT compared to subjects who were on background LLT (− 22.1%, − 23.3% vs. − 17.4%) [41]. Adverse events occurred in 64.1% and 56.8% of subjects in the bempedoic acid and placebo treatment groups, respectively. The most frequent adverse events in the bempedoic acid and placebo groups were muscle related (22.2% and 25.2%, respectively), with the most common one being myalgia, which was experienced by 4.7% in the bempedoic acid group and 7.2% in the placebo group. New-onset or worsening diabetes was less frequently observed in the bempedoic acid group (2.1%) than in the placebo group (4.5%), and among subjects with no history of diabetes, fasting glucose ≥ 126 mg/dL and glycated hemoglobin (HbA1c) ≥ 6.5% were less common with bempedoic acid (6.4% and 4.7%) than with placebo (10.6% and 12.9%). A total of 18.4% of the subjects in the bempedoic acid treatment group discontinued because of an adverse event compared with placebo (11.7%), and myalgia led to study drug discontinuation for 3.4% of subjects who received bempedoic acid and 6.3% of subjects who received

placebo. Patients in the bempedoic acid treatment group did experience a small elevation in mean uric acid levels, but the occurrence rate of gout was low (1.7%) [41]. Overall, bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of adverse events when compared to placebo and led to significantly lower LDL-C levels.

The CLEAR Wisdom study evaluated the long-term efficacy and safety of bempedoic acid 180 mg in high CV-risk subjects receiving maximally tolerated statin with or without other LLT. A total of 799 subjects with pre-existing ASCVD, HeFH, or both who had a baseline fasting LDL-C ≥ 100 mg/dL were randomized 2:1 to treatment with bempedoic acid 180 mg or placebo once daily for 52 weeks in adjunct to background statin therapy with or without additional LLT [42]. The primary endpoint was percentage change in LDL-C from baseline to week 12, and an LS mean percentage change of − 17.4% in LDL-C from baseline was observed, with a − 15.1% reduction in the bempedoic acid group and 2.4% increase with placebo ($p < 0.001$). In addition, a mean LDL-C level of 97.6 mg/L was observed at week 12 in the bempedoic acid group compared with 122.8 mg/dL in the placebo group. The secondary outcome of percentage change in LDL-C at week 24 from baseline compared to placebo was − 14.8% ($p < 0.001$), with a significant LDL-C reduction of − 12.1% in the bempedoic acid group compared to a 2.7% increase in the placebo group ($p < 0.001$). Additional secondary outcomes that were evaluated at week 12 with bempedoic acid versus placebo were also statistically significant and included a mean reduction of − 13.0% for non–HDL-C ($p < 0.001$), − 11.2% for TC ($p < 0.001$), − 13.0% for apoB ($p < 0.001$), and − 8.7% for hsCRP ($p < 0.04$) [42]. Adverse events occurred in 70.1% of subjects in the bempedoic acid group and 70.8% of subjects in the placebo group, with 10.9% in the bempedoic acid group and 8.6% in the placebo group experiencing an adverse event leading to discontinuation of study medication. More than 0.5% of discontinuations were due to myalgia, arthralgia, increased aspartate aminotransferase level, muscle spasm, fatigue, and MI. In subjects randomized to either bempedoic acid or placebo, the occurrence of myalgias was similar (2.9% vs. 3.1%), as was the occurrence of muscle weakness (0.4% for both groups). New-onset or worsening of diabetes occurred in approximately 7% of subjects in both treatment groups, and gout and increased blood uric acid levels were experienced by 2.1% and 2.7% of the subjects in the bempedoic acid group and 0.8% and 0.4% of subjects in the placebo group. Serious adverse events were observed in 20.3% of the treatment group versus 18.7% in the placebo group [36]. In addition, although not significant, major adverse cardiac events (MACE) occurred in 6.1% of subjects in the bempedoic acid group versus 8.2% in the placebo group ($p > 0.05$), with an overall 2% absolute reduction in MACE with bempedoic acid at week 52 [43].

An additional phase 3 study conducted by Ballantyne et al. [44] evaluated the efficacy and safety of bempedoic acid 180 mg and ezetimibe 10 mg fixed-dose combination (FDC) in subjects with hypercholesterolemia at high risk for CVD (defined as presence of ASCVD, HeFH, or multiple CVD risk factors) while still receiving maximally tolerated statin therapy. A total of 382 subjects were enrolled with high CVD risk due to the presence of ASCVD, HeFH, or multiple CVD risk factors. Fasting LDL-C was required to be at least 100 mg/dL for subjects with ASCVD and/or HeFH, or fasting LDL-C had to be > 130 mg/dL for subjects with multiple CVD risk factors. A total of 382 subjects were randomly assigned (2:2:2:1) to once-daily treatment with an FDC of bempedoic acid 180 mg plus ezetimibe 10 mg, bempedoic acid 180 mg alone, ezetimibe 10 mg alone, or placebo for 12 weeks. The primary endpoint of the percentage change in LDL-C from baseline to week 12 for the FDC was significantly greater compared to the ezetimibe, bempedoic acid, and placebo groups ($p < 0.001$ for all). The FDC demonstrated a reduction in LDL-C of − 38.0% compared to placebo ($p < 0.001$). Additionally, a significant proportion of subjects in the FDC treatment group achieved LDL-C levels less than 100 mg/dL or less than 70 mg/dL at week 12 (67.5% and 31.3%) compared to the placebo group (17.5% and 0%; $p < 0.001$), the ezetimibe group (42.5% and 10.0%; $p < 0.002$), and the bempedoic acid monotherapy group (43.9% and 6.1%; $p < 0.003$) [37]. Furthermore, 33.7% of patients in the FDC group had a 50% or more LDL-C reduction from baseline compared to the placebo, ezetimibe, and bempedoic acid groups (0%, 5.0%, 3.7%, $p < 0.001$) at week 12. Key secondary efficacy endpoints of the study included percentage change from baseline to week 12 in hsCRP, non–HDL-C, TC, and apoB. The FDC treatment group had a significant reduction in hsCRP (− 35.1%) compared to the placebo group (21.6%, $p < 0.001$) and the ezetimibe monotherapy group (− 8.2%, $p = 0.002$). However, no statistical significance was observed in subjects receiving bempedoic acid monotherapy compared to the FDC, since a similar reduction of − 31.9% for hsCRP was noted. In relation to other key secondary endpoints, FDC reduced non-HDL-C by − 31.9%, TC by − 26.4%, and apoB − 24.6% versus placebo (1.8%, 0.7%, and 5.5%, $p < 0.001$). Ezetimibe monotherapy lowered non-HDL-C by − 19.9%, TC by − 16%, and apoB by − 15.3% ($p < 0.001$), whereas a similar reduction was seen in the bempedoic acid group: − 14.1%, − 12.1%, and − 11.8% ($p < 0.001$) [44]. Adverse events were reported in 58.7% of all subjects and were more frequently reported in the FDC and bempedoic acid groups than in the ezetimibe or placebo groups. The most common adverse events reported were an increase in uric acid, constipation, fatigue, and muscle spasms, which were all reported in 2.4% of the subjects. In addition, myalgia that led to treatment discontinuation occurred in three

patients in the bempedoic acid monotherapy group and one patient in the ezetimibe group, with no discontinuation in the FDC group [37]. Overall the FDC of bempedoic acid and ezetimibe in addition to background statin therapy demonstrated significant lipid-lowering capabilities compared to placebo or either drug alone.

Cardiovascular outcomes trials (CVOTs) have become increasingly important, demonstrating the effect LLTs have on CV risk reduction. Currently, there is one large phase 3, CV outcomes study, CLEAR Outcomes, that is evaluating the efficacy of bempedoic acid 180 mg compared to placebo on the first occurrence of CV death, MI, nonfatal stroke, or coronary revascularization. The study is examining subjects with high CVD risk who have a baseline LDL-C ≥ 100 mg/dL and are statin intolerant. Enrollment for this study began in 2016, and the study is predicted to be completed by the year 2022 [45]. Important specifics of the CVOT being conducted can be found in Table 3. While this CV outcomes study is crucial for demonstrating CV benefit, there is still a need for a larger variety of patients to be included to be able to increase generalizability. Including patients still on maximally tolerated statin therapy as well as statin intolerant populations would generate more clinically relevant data.

While all LLTs target cholesterol as depicted in Fig. 2, the agents work differently, leading to a variation in side effects and additional positive effects (beyond lowering cholesterol). Statins have the highest rate of myalgias, whereas bempedoic acid and ezetimibe have a very low incidence of myalgias, and PCSK-9 inhibitors have very few to no myalgias associated with their use. Bempedoic acid and statins both lower hsCRP; however, PSCK-9 inhibitors have not yet been shown to lower hsCRP, and ezetimibe has minimal effects on hsCRP. When examining the effects of LLTs on glycemia, statins have been shown to increase the risk of new-onset diabetes and deteriorate glycemic control. However, ezetimibe and PCSK-9 inhibitors have not demonstrated any effect on glycemic control, and neither has bempedoic acid up until this point.

3.4 Safety

The overall safety of bempedoic acid was evaluated and addressed in all its clinical studies and was shown to be well-tolerated. In phase 1 trials, no dose-limiting adverse events were identified. In multiple phase 2 trials, as in phase 1 studies, no significant adverse events were observed with dose escalations. In phase 2a trials, the most common adverse events noted by both Ballantyne et al. [37], and Gutierrez et al. [38], were headaches. Whereas, other phase 2 trials showed myalgia as the most frequently reported, but this did not result in drug discontinuation [46]. In the CLEAR phase 3 studies, bempedoic acid was also shown to be safe, with limited adverse effects. The CLEAR Harmony trial showed an increase in uric acid levels, with no significance for the incidence of MACE with bempedoic acid (4.6%) compared to placebo (5.7%) (95% confidence interval 0.56–1.17) [39]. In the CLEAR Tranquility trial, the incidence of muscle-related adverse events was 3.3% in the bempedoic acid group compared to 3.4% in the placebo group, with the most frequent adverse event observed to be an increase in uric acid levels in the treatment group compare to placebo [40]. In the CLEAR Serenity trial, the most common reported adverse event was myalgia, occurring in 4.7% of subjects in the bempedoic acid group compare to 7.2% in those receiving placebo [41]. The CLEAR Wisdom trial showed that despite subjects being on background statin therapy, the rate of muscle-related adverse events was low and similar in both treatment and placebo groups [42]. The US Prescribing Information of bempedoic acid (Nexletol®)

Table 3 Summary of trial design and inclusion and exclusion criteria for the bempedoic acid cardiovascular outcomes trial (CVOT) [45]

Bempedoic acid CVOT	
Trial design	A randomized, double-blind, placebo-controlled study evaluating the effects of bempedoic acid on the occurrence of major CV events in patients with, or at high risk of developing, CVD who are statin intolerant
	Patients were randomized to either bempedoic acid 180 mg/day or matching placebo
Inclusion criteria	Age between 18 and 85 years
	History of, or at high risk of developing, CVD, including CAD, symptomatic PAD, and cerebrovascular atherosclerotic disease, or at high risk for a CV event
	Patient reported history of statin intolerance (inability to tolerate two or more statins, one at a low dose)
	Fasting blood LDL-C ≥ 100 at screening
Exclusion criteria	Fasting blood TG >500 mg/dL at screening
	Recent (within 90 days of screening) history of major CV events, TIA, or unstable or symptomatic cardiac arrhythmia
	History of severe HF
	Uncontrolled HT or uncontrolled DM

CAD coronary artery disease, *CV* cardiovascular, *CVD* CV disease, *DM* diabetes mellitus, *HF* heart failure, *HT* hypertension, *LDL-C* low-density lipoprotein cholesterol, *PAD* peripheral arterial disease, *TG* triglyceride, *TIA* transient ischemic attack

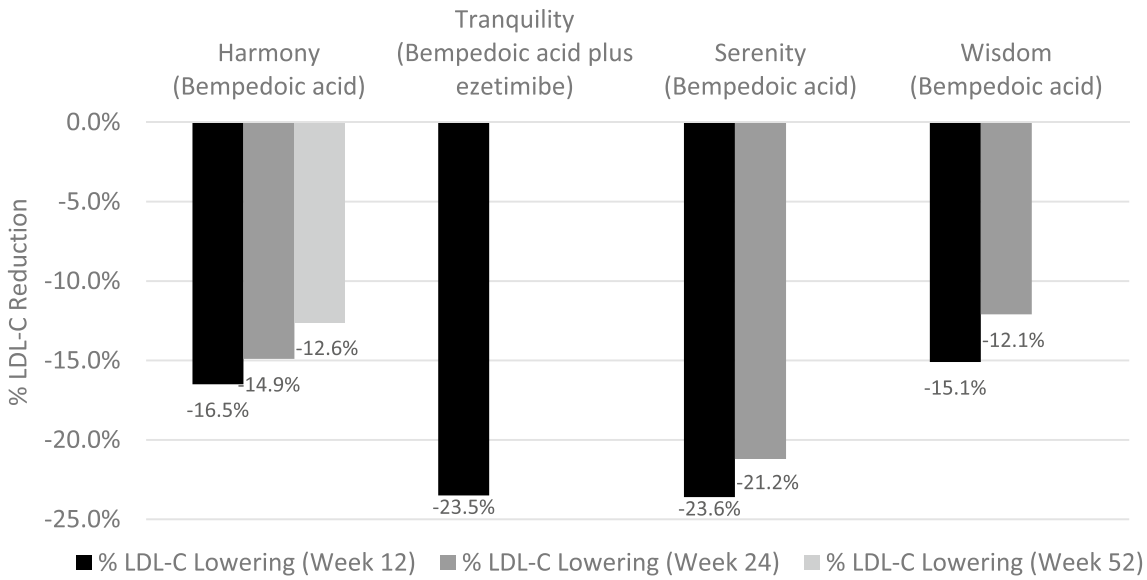

Fig. 2 Comparison of %LDL-C lowering in the CLEAR trials at 12, 24, and 52 weeks [39–42]. *ACL* adenosine triphosphate (ATP)-citrate lyase, *CLEAR* cholesterol lowering through bempedoic acid, an ACL-inhibiting regimen, *LDL-C* low-density lipoprotein cholesterol

[47] warns of hyperuricemia and tendon rupture with the use of the drug.

4 Conclusion

In summary, numerous clinical studies have successfully demonstrated that bempedoic acid as monotherapy or in combination with ezetimibe provides clinical benefit in subjects with hypercholesterolemia. However, the need for a long-term head-to-head trial for CV outcomes with statins, ezetimibe, and PCSK-9 inhibitors remains. Bempedoic acid grants an alternative therapeutic approach for patients who are statin intolerant or who are not able to achieve the desired LDL-C goal of < 100 mg/dL on statin monotherapy. In addition, although bempedoic acid acts on the same pathway as statins, the lack of ACSVL1 in the skeletal muscle prevents its conversion to its active form, which may prevent the muscular adverse events that are associated with statins. In February 2020 the US Food and Drug Administration (FDA) approved the use of bempedoic acid and the combination of bempedoic acid and ezetimibe as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL [47, 48].

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Compliance with Ethical Standards

Conflict of interest Stephanie Niman, Khyatiben Rana, Jessica Reid, Mae Sheikh-Ali, Todd Lewis, Rushab Choksi, and Rebecca Goldfaden declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

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