

## Review Article

# Bempedoic acid: a novel oral LDL-cholesterol lowering agent

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**Abstract:** An elevated LDL-cholesterol is a potent risk factor for atherosclerotic cardiovascular disease (ASCVD). Invariably, pharmacotherapy is required to get high risk patients to goal. The cornerstone of such therapy is the statin class of drugs. Recently Bempedoic Acid (BA), a first in class ATP-citrate lyase inhibitor was approved for LDL-C reduction based on the CLEAR trials in which BA was superior to Placebo. In addition to lowering LDL-C it also lowers apoB and hsCRP levels. BA appears to be very efficacious in combination with ezetimibe especially in statin intolerant patients. However the reduction in LDL-C is modest, it lowers HDL-C levels, causes hyperuricemia and an elevated creatinine. The ongoing Outcomes trial examining ASCVD events with BA will firmly establish the role of BA in our arsenal for the management of ASCVD if positive.

**Keywords:** Hyperlipidemia, bempedoic acid, LDL-cholesterol, uric acid, statin-intolerance, C-reactive protein

### Introduction

Atherosclerotic Cardiovascular Disease (ASCVD) is the leading cause of morbidity and mortality in the western world. Low-density lipoprotein (LDL)-cholesterol is a major risk factor for premature ASCVD. In addition to dietary therapy, exercise, and weight loss, pharmacological therapies are required to lower LDL-C levels in most patients [1]. The cornerstone of therapy is the Hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins). Other effective therapies include ezetimibe, bile acid sequestrants, and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitor therapy [1]. Recently a new oral drug, Bempedoic Acid (BA), was approved by the FDA and European Union for the management of an elevated LDL-C in patients with familial hypercholesterolemia (HeFH) needing further LDL-C lowering despite maximally tolerated statin therapy and also as an adjunct to diet and maximally tolerated statin for secondary prevention of ASCVD to attain LDL-C goals [2, 5]. The European Union also approved BA for patients who are statin intolerant or in whom statins are contra-indicated. In this perspective we briefly discuss its mechanism of action, clinical efficacy, side effect profile, and potential role in the manage-

ment of increased LDL-C levels based on our Pub-Med review.

### Pharmacology

BA is a prodrug that needs to be activated by the enzyme very long-chain acyl-CoA Synthetase-1 (ACSVL1), which is present in liver but not muscle, to bempedoyl-CoA. This active metabolite inhibits ATP citrate lyase (ACL) in the cholesterol biosynthetic pathway upstream of HMG-CoA reductase and thus reduces hepatic cholesterol synthesis [2-5]. ACL provides AcetylCoA as substrate for fatty acid synthesis in addition to cholesterol biosynthesis. This reduced cholesterol synthesis results in an upregulation of LDL receptors on hepatocytes that facilitates clearance of LDL particles from the circulation culminating in an overall decrease in circulating LDL particles [2-5]. Interestingly, BA also increases AMP Kinase activity in various cell types, and this enzyme appears to improve insulin sensitivity [6]. BA is predominantly protein bound (99%) in plasma and has a volume of distribution of 18 L. Major metabolites of BA are glucuronides of BA and bempedoyl-CoA. The enzyme, UDP-glucuronosyltransferase-2B7 (UGT2B7), mediates the process of glucuronidation. BA elimination mainly occurs

in the kidneys with 70% recovery in the urine and 30% recovery in feces. Following administration, BA reaches peak concentration after 3.5 hours, has a half-life of around 21 hours and reaches steady state after 7 days [2-5]. It appears that neither BA, nor its metabolites, are metabolized through P450 enzymes in the liver. Consequently, it does not have interactions with medications such as Warfarin. Notably BA does share drug-drug interactions with Simvastatin and Pravastatin. Co-administration of Bempedoic Acid 180 mg with Simvastatin 40 mg led to a 1.5-fold increase in the area under the curve (AUC) for Simvastatin as well as in peak concentrations. Similarly, BA at a dose of 240 mg when co-administered with Pravastatin 40 mg resulted in a 2-fold increase in the AUC and peak concentration. Drug-drug interactions between BA and Simvastatin and Pravastatin are likely due to inhibitory effects of Bempedoic Acid on the organic acid transporters (OATP) [2]. Hence doses of simvastatin >20 mg and pravastatin >40 mg, in combination with BA therapy, should be avoided to avert myopathy [2, 5].

The mechanism of action of BA is similar to statins since both inhibit cholesterol biosynthesis. Whilst BA inhibits a proximal step, ATP citrate lyase, statins act on the crucial rate limiting step by competitively inhibiting HMG-CoA reductase resulting in greater reduction in LDL-C [1]. PCSK9 inhibitors in contrast bind the protein PCSK9 preventing it from binding LDL receptors since the binding of PCSK9 to LDL receptors targets them for irreversible degradation in the hepatic lysosomes. PCSK9 inhibitors thus preserve LDL receptor recycling allowing for the greater clearance of LDL particles from the circulation [1]. Ezetimibe decreases intestinal and biliary cholesterol absorption by binding to the Niemann-Pick C1-like protein1 and inhibiting this transporter [1]. Bile acid sequestrants bind bile acids in the intestine preventing their absorption by the entero-hepatic circulation resulting in a reduction in LDL-C [1]. Ultimately, all these drugs lower plasma LDL-C by upregulating hepatic LDL receptors.

### Clinical trials

The 4 pivotal trials of clinical efficacy are part of the Cholesterol Lowering via BA, an ACL-inhibiting Regimen (CLEAR) program. They are CLEAR Harmony, CLEAR Wisdom, CLEAR Se-

renity, and CLEAR Tranquility trials [2]. A summary of the salient characteristics of these 4 trials is provided in **Table 1**. All 4 trials were randomized, double-blind, placebo-controlled trials.

The CLEAR Harmony trial explored both the efficacy and tolerability of Bempedoic Acid in 2230 patients who had ASCVD, heterozygous familial hypercholesterolemia (HeFH), or both [7]. To be eligible for the trial, patients needed to be on the maximum tolerated-dose of statin therapy with or without other lipid lowering drugs for at least 4 weeks before screening and have fasting LDL-C of >70 mg/dL. Exclusion criteria included: Triglyceride levels  $\geq$  500 mg/dL, body mass index (BMI)  $\geq$  50 kg/m<sup>2</sup>, history of cardiovascular disease or significant cardiac event in the last 12 weeks, or renal dysfunction/nephrotic syndrome. Patients were randomized in a 2:1 ratio to receive Bempedoic Acid 180 mg/d (n=1488) or placebo (n=742) over the course of 52 weeks. In this trial the mean age of the patients was 66.1 years. The primary end point was safety, and the secondary end point was percentage change in LDL-C at 12 weeks. Whilst adverse events were similar between groups, adverse events leading to discontinuation of regimen was higher with BA (10.9 versus 7.1%); the incidence of gout was also higher with BA, 1.2% vs 0.3%, P=0.03. Importantly, the occurrence of myalgia and muscle weakness was similar between groups. Interestingly, the incidence of new onset or worsening diabetes was reduced in the BA group: 3.3 vs 5.4%, P=0.02. Both serum uric acid and creatinine were significantly increased with BA therapy, P<0.001. Overall reduction of LDL-C from baseline levels was 16.5% at 12 weeks, 18.1% reduction compared to placebo and persisted for the 52 weeks. There were also significant reductions of non-HDL-C, total cholesterol (TC), apolipoprotein B (apoB), and high-sensitivity C-reactive protein (hsCRP) in the Bempedoic Acid Group compared to placebo which were seen at week 12 and sustained for the 52 weeks. Whilst there was a 5.8% reduction in HDL-C compared to placebo, a *p* value was not presented [7].

The CLEAR Wisdom trial was another crucial trial that determined long-term efficacy of Bempedoic Acid in 779 patients with established ASCVD, HeFH, or both [8]. Eligibility criteria included: use of maximal-tolerated dose lip-

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**Table 1.** Salient Characteristics of the CLEAR Clinical Trails

Trial	Sample Size (n) And Study Design	Duration (wks.)	Study Population	Endpoints	Adverse Effects
CLEAR Harmony	n=2230 Randomized and placebo-controlled. BA 180 mg or Placebo	52	ASCVD, HeFH or both on maximum tolerated statin	Overall Safety and Tolerability. Mean LDL-C reduction at 12 weeks compared to baseline was 16.5% with BA Frequency of adverse effects leading to discontinuation of BA was significantly increased in the BA group (10.9%) compared to placebo (7.1%)	Hyperuricemia and Gout Elevated Creatinine Nasopharyngitis Muscle spasms
CLEAR Wisdom	n=779 Randomized and placebo-controlled. BA 180 mg or Placebo	52	ASCVD, HeFH or both on maximum tolerated statin	Percentage change in LDL-C at 12 weeks compared to baseline. BA lowered LDL-C levels by 15.1% compared to baseline at 12 weeks	Urinary Tract Infection Nasopharyngitis Hyperuricemia and Gout Muscle spasms Arthralgias
CLEAR Serenity	n=345 Hypercholesterolemia with statin intolerance Randomized, placebo-controlled. BA 180 mg or Placebo	24	History of intolerance to at least 2 statins	Percentage change in LDL-C at 12 weeks compared to baseline. BA lowered LDL-C levels by 21.4% compared to baseline to 12 weeks	<ul style="list-style-type: none"> <li>• Lower rate of Myalgias compared to Placebo 4.7 vs 7.2%.</li> </ul> Hyperuricemia and Gout Arthralgias Hypertension
CLEAR Tranquility	n=269 Statin intolerant patients with hypercholesterolemia Randomized, placebo-controlled. BA 180 mg or Placebo on Ezetimibe therapy	12	Patients with statin intolerance on ezetimibe therapy -10 mg/d	Percentage change in LDL-C at 12 weeks compared to baseline. BA lowered LDL-C levels by 28.5% compared to placebo from baseline to week 12	<ul style="list-style-type: none"> <li>• Elevated Uric Acid Levels</li> </ul> Elevated transaminases Sinusitis Nasopharyngitis Similar % of muscle-related events 3.3 vs 3.4% with BA vs placebo

id-lowering treatment (did not necessarily have to be a statin) as well as fasting LDL-C level  $\geq 100$  mg/dL at screening and  $\geq 70$  mg/dL 1 week prior to initiation of trial. Patients were randomized in a 2:1 ratio to receive Bempedoic Acid 180 mg/d (n=522) or matched placebo (n=257) for 52 weeks. Both these groups continued lipid lowering therapies that they were on prior to the trial in addition to Bempedoic Acid. If the LDL-C remained greater than 170 mg/dL and elevated by at least 25% from baseline, addition of a new medication or adjustment of dosing of existing medication was allowed. In this trial the mean age of the patients was 64.3 years. The primary end point of the study was percentage change from baseline to week 12 in LDL-C. LDL-C was significantly reduced by 15.1% at week 12 in the Bempedoic Acid group compared to an increase of 2.4% in the placebo arm with a placebo-controlled reduction of 17.4%. These changes were maintained during the study duration of 52 weeks. There were also statistically significant reductions in non-HDL-C, total cholesterol, apoB, and hsCRP levels from baseline to week 12 in the Bempedoic Acid Group, all persisting through 52 weeks except for hsCRP. Interestingly HDL-C levels decreased by 6.1%,  $P < 0.001$  with BA therapy. Nasopharyngitis, urinary tract infections, and hyperuricemia were commoner with BA therapy [8].

Two smaller clinical trials of shorter duration, CLEAR Serenity and CLEAR Tranquility, randomized patients who were unable to take statins at a dose higher than the lowest approved dose into groups that received Bempedoic Acid versus placebo. Patients in both these trials were being treated for both primary or secondary prevention of cardiovascular disease.

In the Clear Tranquility trial the effect of BA on LDL-C was tested in statin intolerant patients (69% not on statin therapy) who required further LDL-C reduction (entry LDL-C  $\geq 100$  mg/dl) [9]. The mean age of the patients was 63.8 years. All patients were on ezetimibe 10 mg/d and were randomized to BA 180 mg/d (n=181) or placebo (n=88) for 12 weeks. Bempedoic Acid decreased LDL-C by 23.5% at 12 weeks compared to baseline and 28.5% when corrected for placebo changes in LDL-C. Secondary endpoints of non-HDL-C, total cholesterol, apoB, and hsCRP also significantly decreased in the group who received Bempedoic Acid

compared to placebo. There was a significant reduction in HDL-C levels of 5.9%,  $P = 0.002$ . The major side effect of note was the greater frequency of elevated uric acid levels. This combination of BA and ezetimibe offers a great alternative for statin intolerant patients [2]. It is important to emphasize that this trial had a short duration of 12 weeks only.

The CLEAR Serenity trial, which was also a phase 3 trial, involved 345 patients with a mean age of 65.2 years with hypercholesterolemia with a history of intolerance to at least 2 statins with one at the lowest available dose [10]. They were randomized to BA (n=234) or placebo (n=111) for 24 weeks. 93% of patients reported a history of statin associated muscle symptoms. In the CLEAR Serenity trial, there was a significant decrease in LDL-C of 21.4% from baseline to 12 weeks when corrected for changes with placebo. In addition there were significant decreases in non-HDL-C, total cholesterol (TC), ApoB and hsCRP levels. Also there was a significant 4.5% reduction in HDL-C in the BA group ( $P = 0.003$ ). Myalgia was reported at a lower rate in the BA group versus placebo, 4.7 vs 7.2%. Also new onset or worsening diabetes was less frequent in the BA group than placebo (2.1 vs 4.5%) [10].

Another important trial that needs to be reported on is a study using the fixed dose combination (FDC) of BA and ezetimibe [11]. In this trial patients with a mean age of 64.3 years with hypercholesterolemia and high risk for ASCVD on stable statin therapy, were assigned to a FDC of BA (180 mg) + ezetimibe (10 mg) (n=108), BA 180 mg (n=110), Ezetimibe 10 mg (n=109), and placebo (n=55). They were followed up for 12 weeks only. The lowering in LDL-C with the FDC at 12 weeks was 36.2% which was greater than ezetimibe (23.2%), BA (17.2%) and placebo (+1.8%),  $P < 0.001$ . The reduction in hsCRP with the FDC was superior to both placebo and ezetimibe but not BA monotherapy: -35.1, +21.6, -8.2 and -31.9% respectively. The safety profile of the FDC was similar to BA and ezetimibe.

### Adverse effects

With all novel therapies it is important to also report on side effects. Common adverse reactions reported with BA include nasopharyngitis, urinary tract infections, muscle spasms and

arthralgias [2-5]. BA could be an attractive alternative to statins given the much lower incidence of myalgia and myopathy-related side effects reported in the CLEAR trials program. A plausible explanation for this phenomena is that ACSVL1, which converts Bempedoic Acid to bempedoyl CoA, is present in the liver and kidneys and not in skeletal muscle, suggesting an advantage in statin-intolerant patients. This has been borne out in 2 CLEAR trials in statin intolerant patients [9, 10].

However, Bempedoic Acid has been associated with increased serum creatinine and uric acid levels, which is possibly due to the fact that it inhibits the organic anion transporter proteins (OATP's) especially in the kidney. It is prudent to assay uric acid levels at baseline in patients prescribed BA and be especially vigilant in patients with hyperuricemia and or a history of gout during follow-up on BA therapy [2-5].

Patients receiving Bempedoic Acid treatment can rarely experience tendon rupture. The patients should be advised of this important adverse reaction at the outset especially those with other risk factors for tendon rupture [2] and told to discontinue therapy with BA immediately if it occurs. Other reported side effects include benign prostate hyperplasia, atrial fibrillation, decreased hemoglobin and leukocyte counts and an increase in blood urea nitrogen and platelet counts. The relevance if any of these side effects will be appreciated in the large ongoing OUTCOMES trial of over >10,000 individuals [2-6]. Also there is no data on the safety of BA in pregnancy [5].

### Conclusion

In conclusion, the large CLEAR Harmony and Wisdom trials with 52 weeks duration clearly establish a role for BA in the management of an elevated LDL-C with other lipid lowering therapies such as statins. Furthermore, the CLEAR Serenity and Tranquility trials provide much needed information on LDL-C lowering and safety of BA in statin-intolerant patients. Finally, the FDC study further endorses the combination of ezetimibe with BA as a very efficacious therapy for reducing LDL-C by 36% if other therapies cannot be used. BA also appears to be anti-inflammatory as manifest by a reduction in hsCRP in all 4 trials. Another perceived

benefit is with respect to mitigating new onset diabetes and worsening glycemic control as reported in some but not all of the CLEAR studies [12]. The concomitant reduction in both LDL-C and hsCRP bodes well for the ongoing OUTCOMES trial. Specifically, this trial will evaluate incidence of major cardiovascular events in a population of patients with history of possible statin-associated side effects and either established cardiovascular disease or at high risk of cardiovascular disease compared to a placebo group. These results are expected to be released in 2023 and will help better position BA in LDL-C lowering regimens if there is a reduction in cardiovascular events. Concerns about the moderate reduction in LDL-C (15-17%) and the decrease in HDL-C [4, 5] can influence clinical outcomes. It would be of interest if lipoprotein (a) levels were reported with BA therapy.

Thus BA, a first in class oral ACL inhibitor, reduces LDL-C moderately compared to statins and PCSK9 inhibitors but appears to be well tolerated in patients with statin intolerance and myalgias. Until the OUTCOMES trial concludes we need to follow the FDA and European Agency recommendations closely.

### Disclosure of conflict of interest

None.

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