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Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia

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IMPORTANCE Additional lipid-lowering therapy options are needed for patients who cannot achieve sufficient decreases in low-density lipoprotein cholesterol (LDL-C) levels using statins alone or for those who are statin intolerant.

OBJECTIVE To conduct a pooled analysis of phase 3 randomized clinical trials of bempedoic acid vs placebo.

DESIGN, SETTING, AND PARTICIPANTS This analysis pooled data from 4 double-blind, placebo-controlled randomized clinical trials conducted from 2016 to 2018. Patients were enrolled in North America and Europe. Eligibility criteria included hypercholesterolemia while receiving stable lipid-lowering therapy and high cardiovascular risk or hypercholesterolemia and statin intolerance.

INTERVENTIONS Patients were randomized 2:1 to bempedoic acid, 180 mg (n = 2425), or placebo (n = 1198) once daily for 12 to 52 weeks.

MAIN OUTCOMES AND MEASURES Primary efficacy end point was percentage change from baseline in LDL-C level at week 12 in the intention-to-treat population. Patients were parsed into 2 groups according to enrollment criteria: (1) patients with hypercholesterolemia and atherosclerotic cardiovascular disease (ASCVD) or with heterozygous familial hypercholesterolemia (HeFH) or with both and receiving statins and (2) patients with hypercholesterolemia who were statin intolerant receiving maximally tolerated statins.

RESULTS In this analysis of 3623 patients, the overall mean (SD) patient age was 65.5 (9.2) years (similar in both pools). Among patients with ASCVD or HeFH or both, the mean (SD) baseline LDL-C level was 107.6 (32.7) mg/dL. At week 12, the LDL-C level percentage change from baseline was −16.0% with bempedoic acid vs 1.8% with placebo (difference, −17.8%; 95% CI, −19.5% to −16.0%; $P < .001$). Patients with statin intolerance had a mean (SD) baseline LDL-C level of 144.4 (38.8) mg/dL. The percentage changes in LDL-C levels at week 12 were −23.0% in the bempedoic acid group and 1.5% in the placebo group (difference, −24.5%; 95% CI, −27.8% to −21.1%; $P < .001$). The decrease in LDL-C levels with bempedoic acid was sustained during long-term follow-up in both pools (patients with ASCVD or HeFH or both receiving a maximally tolerated statin, difference of −12.7% at week 52; patients with statin intolerance, difference of −22.2% at week 24). Decreases in non–high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein levels were greater with bempedoic acid vs placebo. Treatment-emergent adverse events associated more frequently with bempedoic acid than with placebo included increased blood uric acid level (2.1% vs 0.5%), gout (1.4% vs 0.4%), decreased glomerular filtration rate (0.7% vs <0.1%), and increased levels of hepatic enzymes (2.8% vs 1.3%).

CONCLUSIONS AND RELEVANCE Bempedoic acid added to maximally tolerated statins, including moderate- or high-intensity statins or no background statin, was associated with decreased LDL-C levels vs placebo in patients with hypercholesterolemia with an acceptable safety profile. As a nonstatin adjunct or statin alternative, bempedoic acid has potential for use in a broad spectrum of patients.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: NCT02666664, NCT02991118, NCT03001076, and NCT02988115

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Supplemental content

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In the last several decades, the burden of atherosclerotic cardiovascular disease (ASCVD) has decreased in Western populations, in part because of the increasing use of lipid-lowering therapies (LLTs)—most notably statins.[1-3] The decrease in cardiovascular risk with LLTs directly correlates with the extent of the achieved absolute decrease in low-density lipoprotein cholesterol (LDL-C) level.[4] In clinical practice, a large proportion of patients with hypercholesterolemia do not achieve an adequate decrease in LDL-C levels, even with maximally tolerated statin treatment,[5-7] and others experience statin intolerance.[8,9] Additional LLT options are needed to decrease the risk of adverse cardiovascular outcomes in such patients.[8,10]

Bempedoic acid (Esperion Therapeutics Inc) is an oral, once-daily, first-in-class, small molecule that decreases LDL-C level as a consequence of competitive inhibition of adenosine triphosphate-citrate lyase, a key enzyme in the cholesterol biosynthesis pathway upstream of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Inhibition of cholesterol synthesis with bempedoic acid, similar to statins, upregulates hepatic LDL receptor expression, thus decreasing LDL-C blood levels by increasing clearance of circulating LDL-C. Bempedoic acid, a prodrug, requires activation by very long-chain acyl-coenzyme A synthetase-1, an enzyme that is present mainly in the liver but not in skeletal muscle.[11] The lack of skeletal muscle activity of this enzyme is postulated to decrease risk of muscle-related adverse effects with bempedoic acid compared with statin therapy.

Phase 3 randomized clinical trials have shown decreases in LDL-C levels from 17.4% to 28.5% when bempedoic acid was added to stable background LLT, which ranged from no LLT to high-intensity statin treatment with adjunct nonstatin LLT.[12-15] To better understand the extent of the decrease in LDL-C level associated with bempedoic acid administration and the factors that may contribute to the decrease, the present study conducted a pooled analysis of 4 phase 3, placebo-controlled randomized clinical trials of bempedoic acid[12-15] conducted to date.

Key Points

Question Does an association exist between the administration of bempedoic acid and decreased levels of low-density lipoprotein cholesterol in patients with hypercholesterolemia?

Findings In this pooled analysis of 3623 patients included in 4 pivotal randomized clinical trials, bempedoic acid administration was associated with decreased mean low-density lipoprotein cholesterol levels by 18% vs placebo when added to maximally tolerated statin therapy in patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia or both and by 24% vs placebo in patients with a history of statin intolerance. Increased uric acid levels and gout occurred more frequently among patients treated with bempedoic acid than with placebo.

Meaning Treatment with bempedoic acid was associated with decreased levels of low-density lipoprotein cholesterol in patients with hypercholesterolemia when added to background statin therapy and in patients with a history of statin intolerance.

Methods

Study Design

Details of the CLEAR Harmony (A Randomized, Double-blind, Placebo-Controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients With Hyperlipidemia at High Cardiovascular Risk Who Are Not Adequately Controlled by Their Lipid-Modifying Therapy [NCT02666664]),[13] CLEAR Wisdom (A Long-term, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid [ETC-1002] in Patients With Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy [NCT02991118]),[15] CLEAR Tranquility (A Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid [ETC 1002], 180 mg/d, as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C [NCT03001076]),[12] and CLEAR Serenity (A Randomized, Double-blind, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid [ETC-1002], 180 mg, Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients With Elevated LDL-C Who Are Statin Intolerant [NCT02988115])[14] study designs have been reported previously (eTable 1 in the Supplement). These randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 studies were conducted from 2016 to 2018 in accordance with the ethical principles established by the Declaration of Helsinki[16] and Good Clinical Practice guidelines. All protocols were approved by local independent ethics committees at each study site. All study participants provided written informed consent obtained in a manner consistent with the Declaration of Helsinki. No one received compensation or was offered any incentive for participating in these studies.

In all studies, patients with hypercholesterolemia who were receiving stable LLT and who required additional decreases to their LDL-C levels were randomized 2:1 to receive bempedoic acid, 180 mg, or placebo once daily. In the 52-week CLEAR Harmony and CLEAR Wisdom studies, patients were required to have established ASCVD or heterozygous familial hypercholesterolemia (HeFH) or both, be receiving stable maximally tolerated doses of statins with or without other LLT at screening, and have LDL-C levels of 70 mg/dL or more before randomization (to convert LDL-C levels to millimoles per liter, multiply by 0.0259).[13,15] Randomization was stratified by HeFH status and intensity of statin therapy (low, moderate, or high intensity, as shown in eTable 2 in the Supplement). Patients enrolled in the 24-week CLEAR Serenity study and the 12-week CLEAR Tranquility study had a history of statin intolerance and were permitted to be taking only a very low-dose or low-dose statin, respectively (qualifying doses shown in eTable 2 in the Supplement).[12,14] In CLEAR Serenity, patient randomization was stratified by treatment indication (primary vs secondary prevention or HeFH). At screening, the LDL-C level was required to be 130 mg/dL or higher (primary prevention) or 100 mg/dL or higher (secondary prevention and HeFH or either alone). After completing a 4-week placebo

run-in period, patients received double-blind, placebo-controlled study treatment for 24 weeks. In CLEAR Tranquility, patients with LDL-C levels of 100 mg/dL or higher at screening completed a 4-week run-in phase of open-label ezetimibe, 10 mg, daily to confirm tolerance and single-blind placebo added to their existing LLT regimen. Patients were then randomized to 12 weeks of double-blind treatment with bempedoic acid or with placebo added to the background ezetimibe with or without other LLT.

Assessments

The primary efficacy end point in all 4 trials was percentage change from baseline in LDL-C level at week 12. CLEAR Harmony and CLEAR Wisdom also evaluated efficacy for 52 weeks, whereas CLEAR Serenity evaluated efficacy for 24 weeks. All studies evaluated percentage change in fasting plasma lipid levels, including non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol, and apolipoprotein B (apoB) from baseline to week 12 as secondary end points; high-sensitivity C-reactive protein (hsCRP) levels were also evaluated. Lipids were measured at a central clinical laboratory (ICON Laboratory Services Inc) after a fast of 10 or more hours, as previously described.[13] The LDL-C level was calculated using the Friedewald equation; if the level of triglycerides was higher than 400 mg/dL (to convert to millimoles per liter, multiply by 0.0113) or the level of LDL-C was lower than 50 mg/dL, the LDL-C level was measured directly using the Multigent Direct LDL assay (Architect system; Abbott). Total cholesterol level was quantified using the Abbott Architect system, and the non–HDL-C level was determined by subtracting the HDL-C level from the total cholesterol level. The level of apoB was measured using immunonephelometry (BN II system; Siemens Healthcare Diagnostics). The Multigent CRP Vario immunoassay and Abbott Architect system were used to quantify hsCRP. Safety measures included the occurrence of treatment-emergent adverse events (TEAEs).

Statistical Analysis

Efficacy analyses were performed using the intention-to-treat population, including all randomized patients, regardless of the treatment received. To control for differences in patient populations and background therapy, study data were pooled into 2 groups based on the similarity of the study designs. The pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin included data from CLEAR Harmony and CLEAR Wisdom, which enrolled patients with ASCVD, HeFH, or both who were receiving background maximally tolerated statin therapy. In this pool, 97% of patients were receiving a statin, and 91% were receiving a moderate- or high-intensity statin. The statin-intolerant pool included data from CLEAR Tranquility and CLEAR Serenity, which enrolled patients with a history of statin intolerance. In this pool, fewer than 20% of patients were receiving a statin, which was limited to low-dose or very low-dose regimens. Safety analyses were performed on pooled data from all 4 clinical trials and included all randomized patients who received at least 1 dose of study drug.

For primary and secondary efficacy end points (except percentage change from baseline for hsCRP level), an analysis of covariance (ANCOVA) model was used, with study, treatment group, and randomization stratum as factors and relevant baseline value as a covariate for the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin. For the pool of patients with statin intolerance, analyses used a similar ANCOVA model but only included study and treatment group as factors. In the ANCOVA analyses, missing data at week 12 were imputed using a multiple imputation method accounting for treatment adherence. Statistical analyses of percentage change from baseline (least-squares [LS] means and *P* values) were based on the final combined estimators from the Rubin method. For percentage change from baseline in hsCRP level, a nonparametric analysis based on Wilcoxon rank sum test and Hodges-Lehmann estimate of location shift and confidence interval (CI) was performed for both pools. No imputation was performed for missing hsCRP data owing to the extreme skewed distribution. As a sensitivity analysis for LDL-C level decrease across 52 weeks, an on-treatment analysis was performed for the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin that included only those patients who were still receiving assigned study treatment within 7 days before LDL-C level measurement. A *z* test was used to compare differences between LS mean LDL-C level decrease in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin and the pool of patients with statin intolerance. The *P* values for all analyses were 2-sided but nominal and should be considered descriptive.

A planned subgroup analysis of percentage change in LDL-C level from baseline to week 12 was conducted in both pools. The subgroups varied between pools owing to differences in patient populations and background therapy. The covariates in the pool of patients with statin intolerance included age, sex, race, ethnicity, geographic region (North America compared with Europe), baseline body mass index (BMI) calculated as weight in kilograms divided by height in meters squared (<25, 25 to <30, and ≥30), history of diabetes, baseline LDL-C level (<130, 130 to <160, and ≥160 mg/dL), baseline statin use (yes or no), baseline ezetimibe use, and baseline estimated glomerular filtration rate (≥90, 60 to <89, and ≤59 mL/min/1.73 m^2). Race/ethnicity designations were self-reported by patients. For the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, additional parameters included baseline LDL-C level (<100, 100 to <130, and ≥130 mg/dL), HeFH status, prior ASCVD, baseline statin regimen intensity (no, low to moderate, and high), and baseline statin medication (atorvastatin, pravastatin, simvastatin, rosuvastatin, and other). Forest plots were generated to summarize the associated treatment effects as LS mean differences by subgroup. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Patients

The total population comprised 3623 patients: 3009 patients in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin (bempedoic acid, 2010; placebo,

Table 1. Baseline Demographic and Clinical Characteristics of Patients by Treatment Pool

Characteristic	Patients with ASCVD or HeFH receiving statins[a]		Patients with statin intolerance[b]	
	Bempedoic acid (n = 2010)	Placebo (n = 999)	Bempedoic acid (n = 415)	Placebo (n = 199)
Age, mean (SD), y	65.4 (9.06)	66.2 (8.7)	64.6 (10.2)	64.5 (10.2)
Male, No. (%)	1427 (71.0)	697 (69.8)	173 (41.7)	82 (41.2)
Race, No. (%)				
White	1914 (95.2)	960 (96.1)	376 (90.6)	171 (85.9)
Black	66 (3.3)	27 (2.7)	27 (6.5)	20 (10.1)
Other	30 (1.5)	12 (1.2)	12 (2.9)	8 (4.0)
Hispanic ethnicity, No. (%)	67 (3.3)	30 (0.3)	56 (13.5)	27 (13.6)
History, No. (%)				
ASCVD	1952 (97.1)	974 (97.5)	NA	NA
Diabetes	580 (28.9)	293 (29.3)	98 (23.6)	43 (21.6)
Hypertension	1612 (80.2)	818 (81.9)	269 (64.8)	126 (63.3)
BMI, mean (SD)	29.8 (5.0)	29.7 (5.0)	29.9 (5.3)	30.5 (5.4)
eGFR category, mL/min/1.73 m^2, No. (%)				
≥90	427 (21.2)	223 (22.3)	103 (24.8)	33 (16.6)
≥60 to <90	1284 (63.9)	632 (63.3)	249 (60.0)	126 (63.3)
≥30 to <60	298 (14.8)	143 (14.3)	61 (14.7)	40 (20.1)
<30	1 (<0.1)	1 (0.1)	2 (0.5)	0
Background LLT, No. (%)				
Statin alone	1687 (83.9)	837 (83.8)	16 (3.9)	10 (5.0)
Statin plus other LLT	268 (13.3)	133 (13.3)	60 (14.5)	25 (12.6)
Other LLT alone	23 (1.1)	15 (1.5)	206 (49.6)	96 (48.2)
None	32 (1.6)	14 (1.4)	133 (32.0)	68 (34.2)
Baseline statin intensity, No. (%)				
None	55 (2.7)	29 (2.9)	339 (81.7)	164 (82.4)
Low	125 (6.2)	59 (5.9)	76 (18.3)[c]	35 (17.6)[c]
Moderate	811 (40.3)	404 (40.4)	NA	NA
High	1019 (50.7)	507 (50.8)	NA	NA
Baseline ezetimibe use, No. (%)	150 (7.5)	76 (7.6)	215 (51.8)	102 (51.3)
Cholesterol, mean (SD), mg/dL				
Total	185.5 (38.5)	185.4 (40.2)	233.7 (44.7)	226.7 (43.7)
Non-HDL-C	136.1 (37.3)	135.6 (38.3)	179.9 (43.9)	173.4 (43.8)
LDL-C	107.7 (32.3)	107.5 (33.5)	146.0 (39.2)	141.2 (37.7)
HDL-C	49.4 (12.2)	49.8 (12.0)	53.8 (15.4)	53.4 (18.0)
Triglycerides, median (IQR), mg/dL	129 (99.5-172.5)	126.5 (98.5-175.5)	153.0 (112.5-213.0)	150.0 (111.5-194.0)
Apolipoprotein B, mean (SD), mg/dL[d]	95.7 (26.8)	95.0 (28.1)	133.3 (30.7)	130.3 (30.4)
hsCRP, median (IQR), mg/L[e]	1.5 (0.8-3.3)	1.6 (0.83-3.4)	2.5 (1.2-4.7)	2.4 (1.1-4.9)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NA, not applicable.

SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; triglyceride to mmol/L, by 0.0113; apolipoprotein B to g/L, by 0.01.

[a] Includes data from CLEAR Harmony and CLEAR Wisdom, in which bempedoic acid and placebo were administered on a background of maximally tolerated statin use (>97%).

[b] The 2 studies (CLEAR Tranquility [NCT03001076] and CLEAR Serenity [NCT02988115]) in which the statin dose was no more than a low-dose or very low-dose statin.

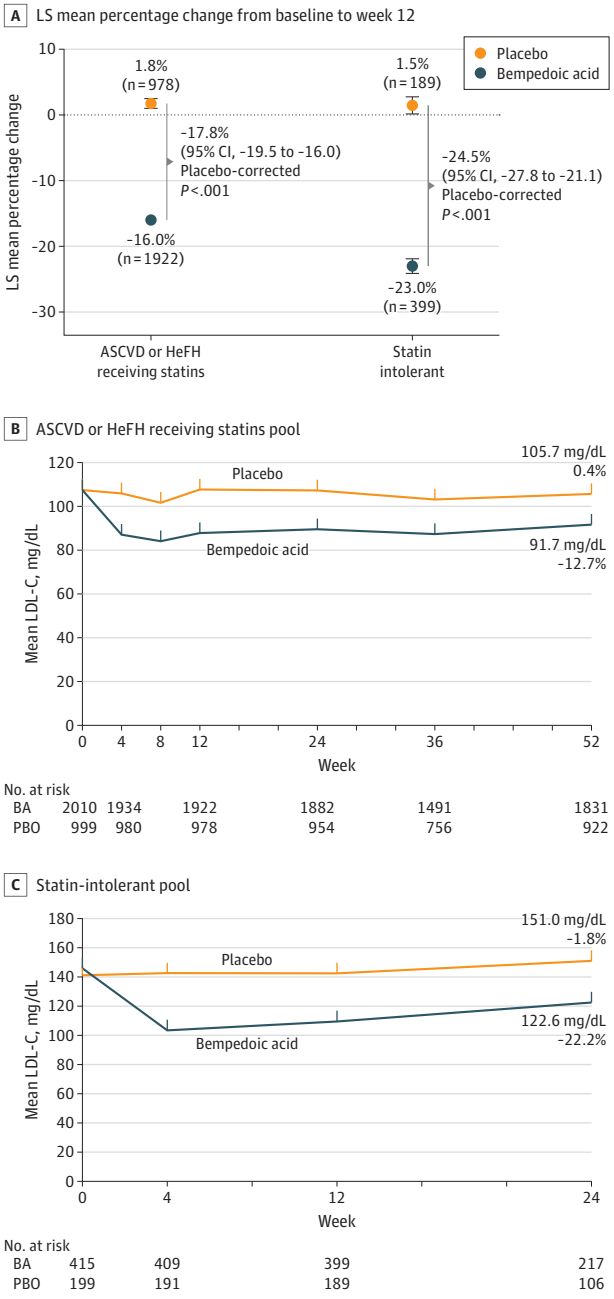
[c] Low-dose or very low-dose statin.

[d] Data available for 2997 patients in the pool of patients with ASCVD and HeFH or with either alone receiving statins (bempedoic acid [n = 993]; placebo [n = 2004]) and 604 patients in the pool with statin intolerance (bempedoic acid [n = 193]; placebo [n = 411]).

[e] Number of patients with ASCVD and HeFH or with either alone receiving statins: bempedoic acid (n = 996) and placebo (n = 2007). Number of patients with statin intolerance: bempedoic acid (n = 192) and placebo (n = 411).

999) and 614 in the pool of patients with statin intolerance (bempedoic acid, 415; placebo, 199) (eFigure 1 in the Supplement). Patient demographic and baseline characteristics were well balanced between the treatment groups for both pools (**Table 1**). Overall, the mean (SD) patient age was 65.5 (9.2) years and was similar in both pools, and the number (%) of males in each group was balanced within the statins pool (bempedoic acid, 1427 [71.0%]; placebo, 697 [69.8%]) and within the pool

Figure 1. Changes in Low-Density Lipoprotein Cholesterol (LDL-C) Levels Associated With Bempedoic Acid Administration



A, Percentage change from baseline in LDL-C levels at week 12. Data are least-squares (LS) mean (SE) values. The difference between placebo-corrected LS mean changes from baseline in LDL-C levels in the pool of patients with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) or both receiving a maximally tolerated statin (−17.8%) and the pool of patients with statin intolerance (−24.5%) was significant (nominal $P < .001$). B and C, Mean LDL-C levels over time by treatment group. Data are observed mean (SE) values through week 52 in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, and through week 24 in the pool of patients with statin intolerance. BA indicates bempedoic acid; PBO, placebo. To convert LDL-C to millimoles per liter, multiply by 0.0259.

of patients with statin intolerance (bempedoic acid, 173 [41.7%]; placebo, 82 [41.2%]). In the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, 2926 (97.2%) patients had a history of ASCVD and 112 (3.7%) had HeFH. In the pool of patients with statin intolerance, 201 patients (32.7%) were receiving no background LLT. In both the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin and the pool of patients with statin intolerance, the prevalence rates of diabetes (patients with ASCVD or HeFH or both receiving a maximally tolerated statin, 873 [29.0%]; patients with statin intolerance, 141 [23.0%]) and hypertension (ASCVD or HeFH or both receiving a maximally tolerated statin, 2430 [80.8%]; patients with statin intolerance, 395 [64.3%]) were high. Baseline lipid parameters, including levels of lipoproteins, were similar between treatment groups for both pools and were consistent with the inclusion criteria. The mean (SD) baseline LDL-C level was 107.6 (32.7) mg/dL in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, and 144.4 (38.8) mg/dL in the pool of patients with statin intolerance.

Primary End Point

Compared with placebo, treatment with bempedoic acid was associated with significantly lower LDL-C levels at week 12 in both pools (**Figure 1**A). The placebo-corrected LS mean changes from baseline in LDL-C levels were −17.8% (95% CI, −19.5% to −16.0%; $P < .001$) in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin (bempedoic acid, −16.0%; placebo, 1.8%) and −24.5% (95% CI, −27.8% to −21.1%; $P < .001$) in the pool of patients with statin intolerance (bempedoic acid, −23.0%; placebo, 1.5%). A test of heterogeneity revealed a significant difference between pools in the placebo-corrected change from baseline at week 12 (nominal $P < .001$).

Secondary and Other Efficacy End Points

The absolute mean decrease from baseline to week 12 in LDL-C level was greater in patients treated with bempedoic acid vs placebo in patients with ASCVD or HeFH or both receiving a maximally tolerated statin (bempedoic acid, −19.8 mg/dL vs placebo, 0.3 mg/dL) and in patients with statin intolerance (bempedoic acid, −36.5 mg/dL vs placebo, 0.6 mg/dL) (eFigure 2 in the Supplement). Decreases in LDL-C were observed at the first postbaseline study visit (week 4) and were maintained through the last measurement time point (bempedoic acid, −12.7% vs placebo, 0.4% at 52 weeks in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin; and bempedoic acid, −22.2% vs placebo, −1.8% at 24 weeks in the pool of patients with statin intolerance; Figure 1B and C). At week 52, the mean LDL-C level in the on-treatment analysis (which included only patients still receiving assigned therapy within 7 days before LDL-C level measurement) was 88.6 (SE, 0.8) mg/dL in the bempedoic acid group vs 104.7 (SE, 1.3) mg/dL in the placebo group, representing LS mean percentage changes from baseline of −15.4 (SE, 0.6) in the bempedoic acid group and −0.1 (SE, 0.8) mg/dL in the placebo group (eFigure 3 in the Supplement). In the on-treatment analysis, decreases from baseline associated with

bempedoic acid vs placebo administration were significant at each time point ($P < .001$). A small but significant attenuation of the associated effect was observed from week 12 to week 52 ($P = .006$).

In the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, a greater percentage of patients in the bempedoic acid group (28.9%) achieved LDL-C levels lower than 70 mg/dL at week 12 compared with placebo (8.0%) ($P < .001$). The proportion of patients with LDL-C levels below 70 mg/dL was consistently higher in the bempedoic acid group (week 24, 28.7%; week 52, 26.2%) than in the placebo group (week 24, 9.3%; week 52, 9.1%) ($P < .001$ for both comparisons). Patients who received bempedoic acid experienced significant placebo-corrected decreases in total cholesterol, non-HDL-C, apoB, and hsCRP levels at week 12, whereas patients in the placebo group experienced increases from baseline for most parameters (eFigure 4 in the Supplement).

Subgroup analyses (**Figure 2**) indicated greater decreases in LDL-C levels associated with bempedoic acid vs placebo treatment for most demographic, disease-related, and background therapy subgroups. The only nonsignificant result was in the small subgroup of Hispanic patients in the pool of patients with statin intolerance. In the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, the results were consistent within subgroup categories based on age, race, ethnicity, geographic region, history of diabetes, baseline LDL-C category, HeFH status, prior ASCVD status, baseline statin intensity, baseline statin medication, background ezetimibe use, and baseline estimated glomerular filtration rate category (Figure 2). Heterogeneity was observed when patients were grouped by sex, with a greater LS mean difference for women vs men, and by BMI category. In the pool of patients with statin intolerance, the results were also consistent within subgroup categories (**Figure 3**), with heterogeneity observed when patients were grouped by ethnicity, history of diabetes, or baseline statin use.

Safety

Treatment-emergent adverse events occurred in 1771 of 2424 patients (73.1%) treated with bempedoic acid and 868 of 1197 patients (72.5%) treated with placebo (**Table 2**). The most common TEAEs were nasopharyngitis, myalgia, and urinary tract infection, which did not differ between treatment groups. Pain in extremity was the only muscle-related term significantly greater in the bempedoic acid group (75 [3.1%] vs 21 [1.8%]; $P = .02$). Rates of other TEAEs of special interest were low and differed in frequency by less than 2% between treatment groups (eg, tendon rupture: bempedoic acid, 0.2% vs placebo, 0; nominal $P = .19$). Nonetheless, the incidence of increased blood uric acid level (2.1% vs 0.5%, nominal $P = .001$), hyperuricemia (1.7% vs 0.6%, nominal $P = .007$), gout (1.4% vs 0.4%, nominal $P = .008$), pain in extremity, decreased glomerular filtration rate (0.7% vs <0.1%, nominal $P = .02$), and increased levels of hepatic enzymes (2.8% vs 1.3%, nominal $P = .004$) were significantly greater in patients treated with bempedoic acid vs placebo, whereas the incidence of new-onset or worsening diabetes was significantly lower in patients treated with bempedoic acid (4.0% vs 5.6%; $P = .03$; nominal $P < .05$). Although the incidence of increased levels of hepatic enzymes was greater in the bempedoic acid group, increases in the levels of transaminases more than 3 times the upper reference limit and more than 5 times the upper reference limit were not significantly different between groups. Laboratory abnormalities typically did not require medical intervention and returned to baseline following discontinuation of treatment.

Treatment-emergent adverse events leading to treatment discontinuation (Table 2) occurred in 273 patients (11.3%) in the bempedoic acid group and 93 patients (7.8%) in the placebo group (nominal $P < .001$). The difference in frequency was not caused by a significant difference between groups in incidence of any single preferred term. Serious TEAEs were reported by 341 patients (14.1%) randomized to bempedoic acid and 159 patients (13.3%) randomized to placebo. No serious TEAEs, including angina pectoris or unstable angina, differed between treatment groups.

Treatment-emergent adverse events with a fatal outcome occurred in 23 patients among 3621 patients in the safety population (bempedoic acid, 19 of 2424 [0.8%]; placebo, 4 of 1197 [0.3%]). All occurred among patients with ASCVD or HeFH or both receiving a maximally tolerated statin and were judged by the investigator and medical monitor as unrelated to study treatment. The difference in occurrence rates between treatment groups resulted primarily from an imbalance in the frequency of cardiac disorders (bempedoic acid, 5 of 1487 [0.3%] vs placebo, 0 of 742) and neoplasms (bempedoic acid, 5 of 1487 [0.3%] vs placebo, 0 of 742) in a single study (CLEAR Harmony). In the companion 52-week study, CLEAR Wisdom, cardiac disorders occurred with greater frequency in the placebo group (2 of 257 [0.8%]) vs bempedoic acid group (3 of 522 [0.6%]), and no fatal neoplasms were reported. Of 5 patients with fatal TEAEs in the neoplasm category in CLEAR Harmony, 3 had an onset within 90 days of first study drug dose. Overall, there was no pattern in the type or temporal nature of the fatalities, which were attributable to the patients' medical history and health at the time of death.

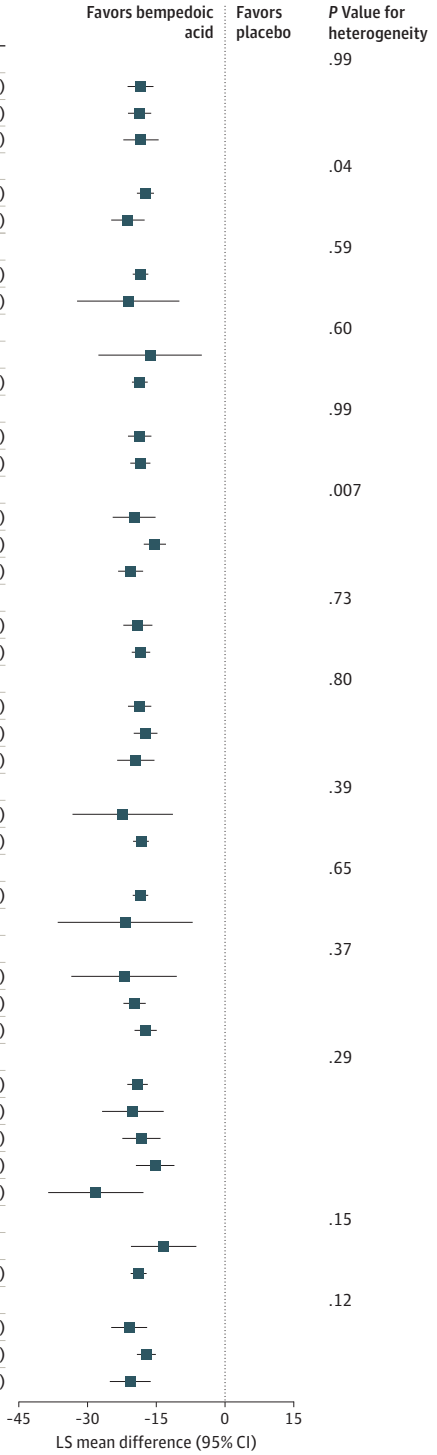
Discussion

In this large pooled analysis encompassing 3623 adults with hypercholesterolemia enrolled in 4 phase 3 randomized clinical trials, treatment with bempedoic acid was associated with significantly decreased LDL-C levels compared with placebo. The decreased LDL-C levels were maintained throughout the treatment period, and were observed on a background of stable LLT, including statins, ezetimibe, or other nonstatin agents. Significant improvements from baseline associated with bempedoic acid administration were also observed for secondary end points, including total cholesterol, non-HDL-C, apoB, and hsCRP levels.

Pooled analyses such as that conducted in the present study provide a tool to address several questions not readily

Figure 2. Percentage Change From Baseline to Week 12 in Low-Density Lipoprotein Cholesterol (LDL-C) by Patients With Atherosclerotic Cardiovascular Disease (ASCVD) or Heterozygous Familial Hypercholesterolemia (HeFH)

Subgroup	Bempedoic acid, No.	Placebo, No.	Placebo-corrected difference (95% CI)	*P* Value for heterogeneity
Age, y				.99
18 to <65	827	374	-18.4 (-21.3 to -15.6)	
65 to <75	800	442	-18.6 (-21.2 to -16.1)	
≥75	295	162	-18.3 (-22.2 to -14.5)	
Sex				.04
Male	1372	685	-17.4 (-19.2 to -15.5)	
Female	550	293	-21.2 (-24.8 to -17.5)	
Race				.59
White	1833	940	-18.4 (-20.1 to -16.7)	
Nonwhite	89	38	-21.1 (-32.3 to -10.0)	
Ethnicity				.60
Hispanic	61	30	-16.3 (-27.6 to -5.0)	
Non-Hispanic	1861	948	-18.6 (-20.3 to -16.9)	
Region				.99
North America	625	324	-18.6 (-21.2 to -16.1)	
Europe	1297	654	-18.5 (-20.7 to -16.3)	
Baseline BMI				.007
<25	292	141	-19.8 (-24.5 to -15.2)	
25 to <30	799	421	-15.3 (-17.7 to -12.9)	
≥30	829	415	-21.1 (-23.8 to -18.4)	
History of diabetes				.73
Yes	553	286	-19.0 (-22.2 to -15.8)	
No	1369	692	-18.3 (-20.3 to -16.3)	
Baseline LDL-C, mg/dL				.80
<100	959	497	-18.6 (-21.2 to -16.1)	
100 to <130	612	297	-17.6 (-20.2 to -15.0)	
≥130	351	184	-19.5 (-23.5 to -15.4)	
Baseline HeFH status				.39
Yes	71	36	-22.3 (-33.3 to -11.4)	
No	1851	942	-18.3 (-20.1 to -16.6)	
Prior ASCVD				.65
Yes	1869	953	-18.4 (-20.1 to -16.7)	
No	53	25	-21.8 (-36.5 to -7.1)	
Baseline statin regimen intensity				.37
No	51	29	-22.0 (-33.5 to -10.5)	
Low/moderate	882	451	-19.7 (-22.2 to -17.3)	
High	989	498	-17.3 (-19.7 to -14.9)	
Baseline statin medication				.29
Atorvastatin	1080	528	-19.1 (-21.3 to -16.8)	
Pravastatin	106	63	-20.1 (-26.8 to -13.4)	
Simvastatin	255	132	-18.2 (-22.4 to -14.1)	
Rosuvastatin	376	209	-15.2 (-19.4 to -11.0)	
Other	54	17	-28.2 (-38.6 to -17.8)	
Baseline ezetimibe use				.15
Yes	144	73	-13.4 (-20.5 to -6.2)	
No	1778	905	-18.8 (-20.6 to -17.1)	
Baseline eGFR category, mL/min/1.73 m^2				.12
≥90	411	217	-20.9 (-24.8 to -17.0)	
60 to 89	1223	621	-17.2 (-19.2 to -15.1)	
≤59	288	140	-20.7 (-25.1 to -16.2)	

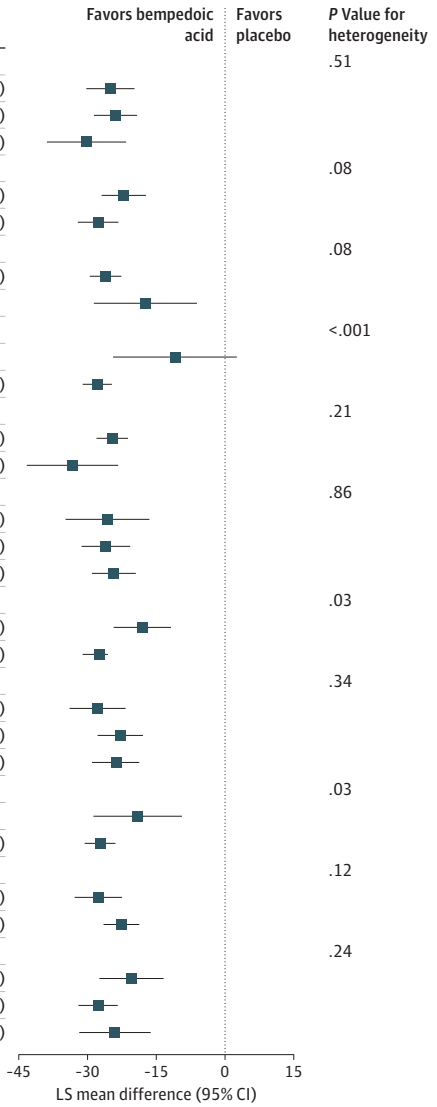


BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; and LS, least squares. To convert LDL-C to millimoles per liter, multiply by 0.0259.

accessible by evaluating individual clinical trial data, such as the consistency of therapeutic efficacy associated with various treatments across patient subgroups and in the safety profile. In general, overall and common adverse events occurred at similar rates in patients treated with bempedoic acid or with placebo. Bempedoic acid has been associated with modest increases in blood uric acid levels,[13,15] and in the present pooled analysis there was a 3.2-fold greater incidence with administration of bempedoic acid (2.1%) vs placebo (0.5%), and a 2.5-fold greater incidence of gout (1.4% vs

Figure 3. Percentage Change From Baseline to Week 12 in Low-Density Lipoprotein Cholesterol (LDL-C) by Patients With Hypercholesterolemia and Statin Intolerance

Subgroup	Bempedoic acid, No.	Placebo, No.	Placebo-corrected difference (95% CI)	*P* Value for heterogeneity
Age, y				.51
18 to <65	172	84	-25.0 (-30.3 to -19.7)	
65 to <75	167	75	-23.9 (-28.6 to -19.2)	
≥75	60	30	-30.2 (-38.8 to -21.5)	
Sex				.08
Male	165	81	-22.1 (-26.9 to -17.2)	
Female	234	108	-27.7 (-32.1 to -23.2)	
Race				.08
White	361	163	-26.1 (-29.5 to -22.6)	
Nonwhite	38	26	-17.4 (-28.6 to -6.1)	
Ethnicity				<.001
Hispanic	54	23	-10.9 (-24.4 to 2.6)	
Non-Hispanic	345	166	-27.9 (-31.0 to -24.7)	
Region				.21
North America	367	175	-24.6 (-28.0 to -21.2)	
Europe	32	14	-33.3 (-43.3 to -23.3)	
Baseline BMI				.86
<25	59	23	-25.6 (-34.8 to -16.5)	
25 to <30	161	82	-26.0 (-31.3 to -20.7)	
≥30	179	84	-24.2 (-29.0 to -19.5)	
History of diabetes				.03
Yes	96	40	-18.0 (-24.3 to -11.8)	
No	303	149	-27.3 (-31.1 to -23.5)	
Baseline LDL-C, mg/dL				.34
<130	152	79	-28.1 (-34.2 to -22.0)	
130 to <160	124	54	-22.8 (-27.8 to -17.9)	
≥160	123	56	-23.8 (-29.0 to -18.7)	
Baseline statin use				.03
Yes	73	32	-19.0 (-28.7 to -9.4)	
No	326	157	-27.2 (-30.6 to -23.9)	
Baseline ezetimibe use				.12
Yes	207	97	-27.6 (-32.8 to -22.5)	
No	192	92	-22.6 (-26.5 to -18.7)	
Baseline eGFR category, mL/min/1.73 m^2				.24
≥90	98	30	-20.4 (-27.4 to -13.4)	
60 to 89	241	121	-27.7 (-32.0 to -23.4)	
≤59	60	38	-24.0 (-31.8 to -16.3)	



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; and LS, least squares. To convert LDL-C to millimoles per liter, multiply by 0.0259.

0.4%, respectively). The increased uric acid levels were typically reversible after bempedoic acid discontinuation. Bempedoic acid inhibits the organic anion transporter 2, which is likely the mechanism responsible for minor increases in uric acid levels.[17] In the US prescribing information, there is a warning and precaution for tendon rupture, indicating that bempedoic acid is associated with an increased risk of tendon rupture based on the assessment by the US Food and Drug Administration of the 2 studies in patients with ASCVD or HeFH.[17] In our analysis, which includes all 4 phase 3 randomized clinical trials, the incidence of tendon rupture was comparable between patients treated with bempedoic acid (0.2%) vs placebo (0); all incidences were judged unlikely or unrelated to treatment by the investigators. Tendon rupture has been reported with statin use,[18,19] extended-release niacin,[20] and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[21] Hypercholesterolemia itself is associated with tendon pathology and increased risk of tendon rupture, particularly among patients with HeFH.[22-24] A causal relationship between bempedoic acid and tendon rupture has not been established. Pain in extremity, a broad term that collates several verbatim terms, was also reported more frequently among patients treated with bempedoic acid vs placebo. This has been noted with the other LLTs included in these studies, including with ezetimibe in the presence or absence of statins.[25]

As a nonstatin adjunct or alternative to statin therapy, bempedoic acid has the potential for use in a broad spectrum of patients; whether it performs equally well in various subgroups, therefore, has clinical importance. In general, a decrease in the LDL-C level associated with bempedoic acid vs placebo administration was consistent in all individual clinical trial subgroup analyses. The results of the present pooled analysis suggested the consistency of the effect associated with

Table 2. Treatment-Emergent Adverse Events

Event	Patients, No. (%)		P value
	Bempedoic acid (n = 2424)	Placebo (n = 1197)	
Overview of TEAEs			
Any	1771 (73.1)	868 (72.5)	.75
Serious	341 (14.1)	159 (13.3)	.54
Associated with study drug	583 (24.1)	243 (20.3)	.01
Drug discontinued due to a TEAE	273 (11.3)	93 (7.8)	.001
With a fatal outcome[a]	19 (0.8)	4 (0.3)	.12
SOC cardiac disorders	8 (0.3)	2 (0.2)	.51
Other	11 (0.5)	2 (0.2)	.24
Most common TEAEs[b]			
Nasopharyngitis	180 (7.4)	106 (8.9)	.15
Urinary tract infection	110 (4.5)	66 (5.5)	.22
Arthralgia	100 (4.1)	57 (4.8)	.39
Upper respiratory tract infection	94 (3.9)	44 (3.7)	.85
Dizziness	83 (3.4)	41 (3.4)	>.99
Diarrhea	82 (3.4)	39 (3.3)	.92
Back pain	75 (3.1)	27 (2.3)	.17
Headache	68 (2.8)	37 (3.1)	.67
Fatigue	54 (2.2)	42 (3.5)	.03
TEAEs of special interest[c]			
Myalgia	118 (4.9)	63 (5.3)	.63
Muscle spasms	89 (3.7)	31 (2.6)	.09
Pain in extremity	75 (3.1)	21 (1.8)	.02
Muscular weakness	13 (0.5)	7 (0.6)	.82
New-onset or worsening diabetes	96 (4.0)	67 (5.6)	.03
Blood uric acid level increase	51 (2.1)	6 (0.5)	<.001
Hyperuricemia	40 (1.7)	7 (0.6)	.007
Gout	33 (1.4)	5 (0.4)	.008
Blood creatinine level increase	19 (0.8)	4 (0.3)	.12
Glomerular filtration rate decrease	16 (0.7)	1 (<0.1)	.02
Hepatic enzyme (ALT or AST) level increase	67 (2.8)	15 (1.3)	.004
>3 Times the upper reference limit	18 (0.7)	3 (0.3)	.10
>5 Times the upper reference limit	6 (0.2)	2 (0.2)	>.99
Neurocognitive disorder	16 (0.7)	9 (0.8)	.83
Hemoglobin decrease	69 (2.8)	22 (1.8)	.07
Anemia	60 (2.5)	19 (1.6)	.09
Hemoglobin level decrease	9 (0.4)	3 (0.3)	.76
Hematocrit decrease	2 (<0.1)	3 (0.3)	.34
Tendon rupture[d]	6 (0.2)	0	.19
Most common TEAEs leading to discontinuation[e]			
Myalgia	31 (1.3)	21 (1.8)	.30
Muscle spasm	18 (0.7)	3 (0.3)	.10
Headache	11 (0.5)	3 (0.3)	.57
Diarrhea	11 (0.5)	1 (<0.1)	.12

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, System Organ Class; TEAEs, treatment-emergent adverse events.

[a] All fatal TEAEs were judged by the investigator and medical monitor as unrelated to treatment.

[b] Occurring in 3% or more of patients in either treatment group, excluding TEAEs of special interest.

[c] TEAEs of special interest were identified a priori (except for tendon rupture) and were derived from nonclinical findings or clinical data for bempedoic acid, adverse events associated with other lipid-lowering therapies, and anticipated adverse events among patients requiring lipid-lowering therapy.

[d] Not prespecified as a TEAE of special interest.

[e] Occurring in 0.5% or more of patients in either treatment group.

bempedoic acid treatment across the majority of demographic and disease-related subgroups, while also suggesting that signals such as greater LDL-C level decreases in women vs men, although modest, warrant further investigation. A small but significant attenuation of the effect associated with treatment was observed over time, similar to results observed with the use of other LLTs.[26]

The aggregate of patient-level data also allowed for the evaluation of the effect associated with background therapy on the decrease in LDL-C levels associated with bempedoic acid treatment. A greater treatment effect was observed among patients in the pool of patients with statin intolerance who were receiving no dose, low-dose, or very low-dose background statin therapy (82% were receiving no background statin), as

evidenced by the greater magnitude of the LDL-C level decrease compared with the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, 91% of whom were receiving a moderate- or high-intensity statin regimen. Attenuation of the magnitude of LDL-C level decrease for patients receiving a statin regimen was not unexpected based on the shared mechanism of inhibition of hepatic cholesterol synthesis by both statins and bempedoic acid. Nonetheless, the additional LDL-C level decrease achieved when bempedoic acid was added to background statin therapy was greater than the anticipated LDL-C level decrease of 5% to 6% that would be achieved by doubling the statin dose.[27] Notably, background ezetimibe therapy, which lowers cholesterol levels via inhibition of Niemann-Pick C1-like intracellular cholesterol transporter 1–mediated intestinal cholesterol absorption and subsequent upregulation of LDL receptor expression by the liver, did not attenuate LDL-C lowering with bempedoic acid. Indeed, data from a recent randomized clinical trial of a fixed-dose combination of bempedoic acid and ezetimibe indicated that the decrease in LDL-C levels with the combination of these agents is additive.[28]

The absolute mean decreases in LDL-C levels associated with bempedoic acid administration were 19.8 mg/dL in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin and 36.5 mg/dL in the pool of patients with statin intolerance. These decreases are of sufficient magnitude to provide meaningful changes in the cardiovascular risk profile. Using the Cholesterol Treatment Trialists' Collaboration estimate of major vascular event risk reduction per 1.0 mmol/L–LDL-C decrease,[1] the corresponding decreases in event risk with bempedoic acid would theoretically be 11% and 21%, respectively, in the setting of a 5-year cardiovascular outcomes trial. The actual translation of LDL-C level decrease with bempedoic acid administration into cardiovascular protective effects is being evaluated in the ongoing CLEAR Outcomes study.[29]

The characteristics of patients who comprised the 2 pools in the present analysis have relevance to clinical practice because these are groups for whom nonstatin agents are a guideline-recommended treatment option. According to the 2018 American College of Cardiology/American Heart Association guideline on the management of blood cholesterol,[30] addition of the nonstatin agent ezetimibe is recommended for patients with ASCVD whose LDL-C level remains 70 mg/dL or higher despite maximally tolerated statin therapy. Addition of a PCSK9 inhibitor to maximally tolerated statin therapy plus ezetimibe may be considered in very high-risk patients,[30] but access to these drugs has been limited.[31] An alternative such as bempedoic acid has the potential to fulfill an unmet clinical need for high-risk patients in whom the administration of a statin or a statin plus ezetimibe does not adequately decrease LDL-C levels and for patients with statin intolerance.

Limitations

There are several limitations to consider when evaluating a pooled analysis. Data pooled for this analysis were derived from 4 studies, with different durations, eligibility criteria, and patient demographic characteristics and comorbidities, increasing the potential for heterogeneity and variability in the data set. In addition, background LLT was highly variable both within and across studies, and adherence to background LLT was not monitored. The latter point may explain the slight increase in LDL-C levels observed at later measurement time points. The size of some of the subgroups analyzed was relatively small. Further investigations of key subgroups and safety end points are warranted.

Conclusions

The results of the present pooled analyses suggest that the addition of bempedoic acid administration to stable background LLT, including the use of moderate- or high-intensity statin regimens, was associated with significantly lower LDL-C levels compared with placebo in patients with hypercholesterolemia.

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Acquisition, analysis, or interpretation of data: Banach, Duell, Leiter, Mancini, Ray, Flaim, Ye, Catapano.
Drafting of the manuscript: Duell, Gotto, Laufs, Mancini.
Critical revision of the manuscript for important intellectual content: All authors.
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Administrative, technical, or material support: Banach, Gotto.
Supervision: Banach, Duell, Gotto, Mancini, Ray, Flaim.

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