ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

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This article was updated on March 19, 2019, at NEJM.org.

N Engl J Med 2019;380:1022-32.
DOI: 10.1056/NEJMoa1803917

ABSTRACT

BACKGROUND

Short-term studies have shown that bempedoic acid, an inhibitor of ATP citrate lyase, reduces levels of low-density lipoprotein (LDL) cholesterol. Data are limited regarding the safety and efficacy of bempedoic acid treatment in long-term studies involving patients with hypercholesterolemia who are receiving guideline-recommended statin therapy.

METHODS

We conducted a randomized, controlled trial involving patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. Patients had to have an LDL cholesterol level of at least 70 mg per deciliter while they were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy. (Maximally tolerated statin therapy was defined as the highest intensity statin regimen that a patient was able to maintain, as determined by the investigator.) Patients were randomly assigned in a 2:1 ratio to receive bempedoic acid or placebo. The primary end point was safety, and the principal secondary end point (principal efficacy end point) was the percentage change in the LDL cholesterol level at week 12 of 52 weeks.

RESULTS

The trial involved 2230 patients, of whom 1488 were assigned to receive bempedoic acid and 742 to receive placebo. The mean (±SD) LDL cholesterol level at baseline was 103.2±29.4 mg per deciliter. The incidence of adverse events (1167 of 1487 patients [78.5%] in the bempedoic acid group and 584 of 742 [78.7%] in the placebo group) and serious adverse events (216 patients [14.5%] and 104 [14.0%], respectively) did not differ substantially between the two groups during the intervention period, but the incidence of adverse events leading to discontinuation of the regimen was higher in the bempedoic acid group than in the placebo group (162 patients [10.9%] vs. 53 [7.1%]), as was the incidence of gout (18 patients [1.2%] vs. 2 [0.3%]). At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg per deciliter, representing a change of –16.5% from baseline (difference vs. placebo in change from baseline, –18.1 percentage points; 95% confidence interval, –20.0 to –16.1; P<0.001). Safety and efficacy findings were consistent, regardless of the intensity of background statin therapy.

CONCLUSIONS

In this 52-week trial, bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse events than placebo and led to significantly lower LDL cholesterol levels. (Funded by Esperion Therapeutics and the NIHR Imperial Biomedical Research Centre; CLEAR Harmony ClinicalTrials.gov number, NCT02666664.)

Lipid-lowering therapies, primarily statins, have substantially reduced the burden of cardiovascular disease over the past three decades.[1] However, statin therapy alone is often insufficient to achieve appropriate lowering of the low-density lipoprotein (LDL) cholesterol level.[2,3] Hence, many patients have a cholesterol level that is not at goal for their level of perceived risk.[4,5] A clinical need exists for the development of additional therapies that are both safe and effective in lowering the LDL cholesterol level to complement existing therapies.

Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is a small molecule that has been shown to lower the LDL cholesterol level by inhibiting ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway that acts upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target for statins (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Bempedoic acid is a prodrug and requires activation by the enzyme very-long-chain acyl-CoA synthetase 1, which is present in the liver but absent in most peripheral tissues.[6] Therefore, an important feature differentiating bempedoic acid from statins is its liver-specific action.[6] Previous studies involving up to 250 patients who were treated for up to 12 weeks have shown that bempedoic acid is effective and has an apparently good safety profile.[7-11] Here, we present the results of the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Harmony trial, a phase 3 trial of bempedoic acid, in which we assessed safety and efficacy data over a 1-year intervention period.

Methods

Trial Design and Oversight

We conducted a 52-week, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial. The objective was to assess the safety, side-effect profile, and efficacy of bempedoic acid therapy when it was added to the use of maximally tolerated statins for 1 year. Maximally tolerated statin therapy was defined as the highest intensity statin regimen that a patient was able to maintain, as determined by the investigator on the basis of clinical judgment and the patient's history.

The trial protocol (available at NEJM.org) was approved by an institutional review board or independent ethics committee at each participating institution. All the trial participants provided written informed consent.

The first author wrote the first draft of the manuscript, and all the authors had access to the data, participated in revising the manuscript, and concurred with the decision to submit the manuscript for publication. Medical writing and editorial assistance in the preparation of the manuscript was provided by JB Ashtin, a medical communications company, and funded by the sponsor, Esperion Therapeutics. The sponsor, with guidance from the steering committee, was involved in the design and conduct of the trial, in the data collection and analysis, and in the manuscript development process. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Adults with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both were eligible to participate if they had been taking stable doses of maximally tolerated statin therapy either alone or in combination with other lipid-lowering therapies for at least 4 weeks before screening and if they had a fasting LDL cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter) during a 2-week screening period. Key exclusion criteria were the use of gemfibrozil or simvastatin at doses greater than 40 mg per day (although high-intensity atorvastatin and rosuvastatin regimens were permitted). The use of any inhibitor of proprotein convertase subtilisin–kexin type 9 (PCSK9) was prohibited starting 4 weeks before trial entry but was permitted after trial week 24 if the LDL cholesterol level was greater than 170 mg per deciliter (4.4 mmol per liter) and had increased by at least 25% from baseline. These criteria were evaluated by a staff member at the central laboratory who was not involved in the trial and who was unaware of the trial-group assignments; all others (investigators, staff, and patients) were unaware of the lipid levels (as well as the trial-group assignments and outcomes) throughout the trial (see the Supplementary Appendix).

Trial Procedures

Randomization was stratified according to the intensity of statin therapy at baseline (low, mod-

erate, or high[2]) (see Section 4.3 in the Supplementary Appendix) and the presence or absence of heterozygous familial hypercholesterolemia. Patients were randomly assigned in a 2:1 ratio to receive either bempedoic acid (at a dose of 180 mg once daily) or matching placebo. Follow-up visits were conducted at weeks 4, 8, 12, 24, 36, and 52 and included the obtaining of fasting blood samples for biomarker measurement. (Laboratory analytical methods are discussed in Section 4.6 in the Supplementary Appendix.)

END POINTS

The primary end point of the trial was overall safety, which was assessed according to the incidence of adverse events and changes in safety laboratory variables. The severity of adverse events and their relation to the trial agent were classified according to protocol criteria by the site investigator. Reported verbatim terms were coded to preferred term and system-organ class with the use of the *Medical Dictionary of Regulatory Activities* (MedDRA), version 20.1. Designated clinical end points, including major adverse cardiac events, were adjudicated centrally by an independent expert committee whose members were unaware of the trial-group assignments. Monitoring of adverse events that occurred during the intervention period was conducted from the receipt of the first dose through 30 days after the receipt of the last dose of trial agent.

The principal secondary end point (principal efficacy end point) was the percentage change in the LDL cholesterol level from baseline to week 12. Additional key secondary end points were the percentage changes in the levels of non–high-density lipoprotein (non-HDL) cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein from baseline to week 12.

STATISTICAL ANALYSIS

We chose a priori to use a sample of 1300 patients in the bempedoic acid group and 650 patients in the placebo group with 52-week follow-up so the trial would provide sufficient long-term exposure to the bempedoic acid program. We calculated that this sample size would allow the trial to identify an excess relative risk of 2.0 regarding adverse events occurring at rates between 1.6% and 13.6% in the placebo group (the 95% confidence interval excludes 1). We estimated that the sample size would also allow the trial to detect rare events at an incidence as low as 0.5% in the bempedoic acid group.

All the patients who received at least one dose of bempedoic acid or placebo were included in the safety analysis (safety population). All the safety data were analyzed with the use of descriptive statistics and were reported as observed, with no imputation of missing data. Efficacy analyses for the principal secondary end point were performed in the intention-to-treat population, which included all the patients who underwent randomization. Key efficacy end points were included in a step-down testing procedure to control the overall type 1 error (see Section 4.8 in the Supplementary Appendix). Missing data for these end points were imputed with the use of a pattern-mixture model. Analysis of covariance (ANCOVA) was used for the efficacy end points involving percentage change, with trial group and randomization strata as factors and with baseline value as a covariate. Because of its nonnormal distribution, the level of high-sensitivity C-reactive protein was analyzed with the use of a nonparametric analysis (Wilcoxon rank-sum test) with Hodges–Lehmann estimates and 95% confidence intervals. The percentage changes in lipid variables and biomarkers at other time points (weeks 24 and 52) and the assessment of the principal efficacy end point in subgroups of patients were analyzed with the use of ANCOVA without imputation (i.e., with observed data). Sensitivity analyses were performed for efficacy measures, including observed-data and on-treatment analyses; the on-treatment analyses excluded efficacy data that were collected more than 7 days after the last dose of trial agent.

Analyses were performed with the use of SAS software, versions 9.2 and later (SAS Institute). Full details of the statistical analysis plan are provided with the protocol.

RESULTS

CHARACTERISTICS OF THE PATIENTS

We conducted this phase 3 trial between January 18, 2016, and February 21, 2018. A total of 3395 patients underwent screening, of whom 2230 underwent randomization at 114 sites in five countries. A total of 1488 patients were randomly assigned to receive bempedoic acid and

742 to receive placebo. Of these, 78.1% of the patients (1142 patients in the bempedoic acid group and 600 in the placebo group) completed the intervention, and 94.6% (1404 patients in the bempedoic acid group and 706 in the placebo group) continued in the trial through the week 52 visit (Fig. S2 in the Supplementary Appendix), which yielded a total of 1247.5 patient-years of exposure to bempedoic acid.

In the overall trial population, the mean age of the patients was 66.1 years. A total of 1628 patients (73.0%) were men, 2139 (95.9%) were white, 2176 (97.6%) had a history of atherosclerotic cardiovascular disease, and 79 (3.5%) had heterozygous familial hypercholesterolemia (Table 1). Regarding background use of statin therapy, among the 2230 patients in the trial, 148 (6.6%) used low-intensity therapy, 970 (43.5%) used moderate-intensity therapy, and 1112 (49.9%) used high-intensity therapy. A total of 172 patients (7.7%) were receiving ezetimibe either alone or in combination with statins, and 80 patients (3.6%) were receiving fibrates. The mean (±SD) LDL cholesterol level at baseline was 103.2±29.4 mg per deciliter (2.67±0.76 mmol per liter).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Bempedoic Acid (N=1488)	Placebo (N=742)
Age — yr	65.8±9.1	66.8±8.6
Male sex — no. (%)	1099 (73.9)	529 (71.3)
White race — no. (%)†	1423 (95.6)	716 (96.5)
Cardiovascular risk factor — no. (%)		
Atherosclerotic cardiovascular disease	1449 (97.4)	727 (98.0)
Heterozygous familial hypercholesterolemia	56 (3.8)	23 (3.1)
Diabetes	425 (28.6)	212 (28.6)
Hypertension	1174 (78.9)	594 (80.1)
Lipid measures at baseline — mg/dl		
Total cholesterol‡	179.7±35.1	178.6±35.6
LDL cholesterol‡	103.6±29.1	102.3±30.0
Non-HDL cholesterol‡	130.9±33.7	129.4±33.9
HDL cholesterol‡	48.7±11.9	49.3±11.5
Apolipoprotein B§	88.5±21.6	86.8±21.8
Triglycerides — mg/dl¶		
Median	126	123
Interquartile range	98–166	96–170
High-sensitivity C-reactive protein — mg/liter‖		
Median	1.49	1.51
Interquartile range	0.74–3.28	0.79–3.33
Concomitant lipid-modifying therapy — no. (%)		
Statin	1485 (99.8)	742 (100)
Ezetimibe	116 (7.8)	56 (7.5)
Fibrate	54 (3.6)	26 (3.5)
None	2 (0.1)	0
Intensity of statin therapy at baseline — no. (%)		
Low	100 (6.7)	48 (6.5)
Moderate	646 (43.4)	324 (43.7)
High	742 (49.9)	370 (49.9)

* Plus–minus values are means ±SD. For the levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, triglycerides, and total cholesterol, baseline was defined as the mean of the values at screening and before receipt of the dose on trial day 1; for other variables, baseline was defined as the last value before the first dose of trial agent. In a post hoc analysis to provide descriptive statistical comparisons, there were no significant differences between the two groups in the baseline characteristics, except for age (P=0.02); the difference in age between the two groups was not considered to be clinically important. Percentages may not add up to 100 because of rounding.
† Race was reported by the patient.
‡ To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
§ Data were available for 1485 patients in the bempedoic acid group and for 736 in the placebo group.
¶ To convert values for triglycerides to millimoles per liter, multiply by 0.01129.
‖ Data were available for 1487 patients in the bempedoic acid group and for 739 in the placebo group.

SAFETY

A total of 2229 patients (1487 in the bempedoic acid group and 742 in the placebo group) were included in the safety analysis. One patient in the bempedoic acid group underwent randomization in error and did not receive any dose of the medication; this patient was excluded from the safety population. The incidence of adverse events according to category and specific events (part of the primary end point of safety) is shown in Table 2. Adverse events that occurred during the intervention period, regardless of causality, were reported in 1167 patients (78.5%) receiving bempedoic acid and in 584 (78.7%) receiving placebo, with the majority of events (in 982 of 1167 patients [84.1%] and 514 of 584 [88.0%], respectively) being graded as mild to moderate. The incidence was similar when assessed according to system-organ class. The most common adverse events (occurring in >4% of the patients in either group) were nasopharyngitis, myalgia, upper respiratory tract infection, urinary tract infection, arthralgia, dizziness, muscle spasms, and diarrhea, which occurred with similar frequency in the two groups (Table S3 in the Supplementary Appendix).

Table 2. Adverse Events and Key Safety Laboratory Findings.*

Variable	Bempedoic Acid (N=1487)	Placebo (N=742)	P Value†
Adverse events			
Any adverse event — no. (%)	1167 (78.5)	584 (78.7)	0.91
Serious adverse event — no. (%)	216 (14.5)	104 (14.0)	0.80
Leading to discontinuation of trial agent — no. (%)	162 (10.9)	53 (7.1)	0.005
Death — no. (%)	13 (0.9)	2 (0.3)	0.17
Adjudicated major adverse cardiac event — no. (%)	68 (4.6)	42 (5.7)	0.30
Death from cardiovascular causes	6 (0.4)	1 (0.1)	0.44
Nonfatal myocardial infarction	19 (1.3)	13 (1.8)	0.45
Nonfatal stroke	5 (0.3)	2 (0.3)	1.00
Coronary revascularization	38 (2.6)	24 (3.2)	0.41
Hospitalization for unstable angina	14 (0.9)	11 (1.5)	0.29
Other major adverse cardiac event–related event — no. (%)			
Death from noncardiovascular causes	2 (0.1)	1 (0.1)	1.00
Noncoronary arterial revascularization	4 (0.3)	6 (0.8)	0.09
Hospitalization for heart failure	9 (0.6)	1 (0.1)	0.18
Event of special interest — no. (%)			
Muscular disorder	195 (13.1)	75 (10.1)	0.05
Muscular disorder leading to discontinuation of trial agent	31 (2.1)	14 (1.9)	0.87
Myalgia	89 (6.0)	45 (6.1)	0.92
Muscle spasms	62 (4.2)	20 (2.7)	0.09
Pain in extremity	50 (3.4)	16 (2.2)	0.14
Muscular weakness	9 (0.6)	4 (0.5)	1.00
New-onset or worsening diabetes	49 (3.3)	40 (5.4)	0.02
Gout	18 (1.2)	2 (0.3)	0.03
Increase in blood creatinine level	12 (0.8)	3 (0.4)	0.41
Decrease in glomerular filtration rate	8 (0.5)	0	0.06
Neurocognitive disorder	11 (0.7)	7 (0.9)	0.62
Laboratory results			
Alanine or aspartate aminotransferase level >3× ULN — no. (%)‡	7 (0.5)	1 (0.1)	0.28
Creatine kinase level >5× ULN — no. (%)‡	7 (0.5)	1 (0.1)	0.28
Change from baseline in uric acid level — mg/dl§	0.73±1.11	−0.06±0.87	<0.001
Creatinine level¶			
Change from baseline — mg/dl	0.02±0.13	−0.02±0.12	<0.001
Change from baseline of >1 mg/dl — no. (%)	2 (0.1)	0	1.00
Estimated glomerular filtration rate <30 ml/min/1.73 m^2 — no. (%)	14 (0.9)	3 (0.4)	0.20

* Plus–minus values are means ±SD. Data include events that occurred from the first dose through 30 days after the last dose of trial agent.

† P values were calculated without adjustment for multiple comparisons and are provided for descriptive purposes only. P values were calculated by a two-sided Fisher's exact test for proportions and a two-sample Welch's t-test for change-from-baseline data. A P value of less than 0.05 was considered to indicate statistical significance.

‡ Events included elevations of more than 3 times the upper limit of the normal range (ULN) for the aminotransferase levels or 5 times the ULN for the creatine kinase level that had been repeated and confirmed.

§ Data were available from baseline to week 52 for 1358 patients in the bempedoic acid group and for 680 in the placebo group. To convert values for uric acid to micromoles per liter, multiply by 59.48.

¶ Data were available from baseline to week 52 for 1343 patients in the bempedoic acid group and for 677 in the placebo group. To convert values for creatinine to micromoles per liter, multiply by 88.4.

The incidence of reported serious adverse events was generally small and similar in the two groups (216 patients [14.5%] in the bempedoic acid group and 104 [14.0%] in the placebo group). However, the percentage of patients who discontinued the blinded trial regimen owing to a reported adverse event was higher in the bempedoic acid group than in the placebo group (162 patients [10.9%] vs. 53 [7.1%]). The percentages of patients who discontinued the regimen owing to muscle-related adverse events were low in the two groups (31 patients [2.1%] in the bempedoic acid group and 14 [1.9%] in the placebo group).

Death occurring within 30 days after the last dose of trial agent was reported in 13 patients (0.9%) in the bempedoic acid group and in 2 (0.3%) in the placebo group. Of the 13 deaths in the bempedoic acid group, 5 were attributable to cancer (4 patients with lung cancer and 1 patient with liver metastases of unknown primary origin), which was generally diagnosed early during the course of the trial (3 cases were diagnosed within 90 days after the initiation of the trial regimen). Of the remaining deaths, 5 were due to cardiac causes in patients with an extensive history of coexisting vascular disease (2 deaths from cardiac failure, 2 from myocardial infarction, and 1 from hypertensive heart disease), and 1 each was due to sepsis after a cholecystectomy, pancreatic pseudocyst, and ischemic cerebral infarction. All 15 deaths were judged by the trial site investigator, who was unaware of the trial-group assignments, as being unlikely to be related or not related to the trial agent.

A total of 110 patients had at least one event that was centrally adjudicated as a major adverse cardiac event, with such events occurring in 68 patients (4.6%) in the bempedoic acid group and in 42 (5.7%) in the placebo group (Table 2). Adverse events that were categorized as cardiac disorders occurred in 157 patients (10.6%) in the bempedoic acid group and in 86 (11.6%) in the placebo group. The incidence of repeated and confirmed elevations in aminotransferase levels (>3 times the upper limit of the normal range) and the creatine kinase level (>5 times the upper limit of the normal range) was relatively low in the two groups (7 patients [0.5%] in the bempedoic acid group and 1 [0.1%] in the placebo group for aminotransferase levels; and in 7 [0.5%] and 1 [0.1%], respectively, for the creatine kinase level). All elevations in aminotransferase levels were transient and abated regardless of whether the trial agent was continued or discontinued.

The occurrence of muscle-related adverse events of importance (myalgia and muscular weakness) was similar in the two groups, whereas gout occurred more commonly in the bempedoic acid group than in the placebo group (18 patients [1.2%] vs. 2 [0.3%]). Uric acid levels increased slightly and the estimated glomerular filtration rate decreased slightly after the initiation of bempedoic acid therapy, but the latter increased over time (Fig. S3 in the Supplementary Appendix). The incidence of new-onset diabetes or worsening of diabetes was lower in the bempedoic acid group than in the placebo group (49 patients [3.3%] vs. 40 [5.4%]). The frequency of adverse events did not appear to differ substantially according to the intensity of background statin therapy (Table 3).

EFFICACY

At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg per deciliter (0.50 mmol per liter). Treatment with bempedoic acid resulted in greater lowering of the LDL cholesterol level than was observed in the placebo group both at week 12 (difference, –18.1 percentage points; 95% confidence interval [CI], –20.0 to –16.1; P<0.001) and at week 24 (difference, –16.1 percentage points; 95% CI, –18.2 to –14.0; P<0.001). The differences in the changes from baseline, as compared with placebo, in the levels of non-HDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein at week 12 were –13.3 percentage points (95% CI, –15.1 to –11.6), –11.1 percentage points (95% CI, –12.5 to –9.8), –11.9 percentage points (95% CI, –13.6 to –10.2), and –21.5 percentage points (95% CI, –27.0 to –16.0), respectively (P<0.001 for all comparisons) (Table S5 in the Supplementary Appendix). Results were consistent in the on-treatment analysis (Table S6 in the Supplementary Appendix).

The majority of patients in the bempedoic acid group had a reduction in the LDL cholesterol level (Fig. S4 in the Supplementary Appendix). The effects of bempedoic acid were still apparent through week 52 (Fig. 1), with minimal attenuation of effect in the on-treatment analyses over the period of 52 weeks (Fig. S5 in the Supplementary Appendix). Efficacy did not vary according to the type or intensity

Table 3. Adverse Events According to Intensity of Background Statin Therapy.*

Event	Low Intensity		Moderate Intensity		High Intensity	
	Bempedoic Acid (N=99)	Placebo (N=47)	Bempedoic Acid (N=652)	Placebo (N=327)	Bempedoic Acid (N=736)	Placebo (N=368)
	number of patients (percent)					
Any adverse event	80 (80.8)	37 (78.7)	513 (78.7)	259 (79.2)	574 (78.0)	288 (78.3)
Serious adverse event	15 (15.2)	5 (10.6)	89 (13.7)	46 (14.1)	112 (15.2)	53 (14.4)
Muscle-related adverse event†	22 (22.2)	8 (17.0)	84 (12.9)	36 (11.0)	89 (12.1)	31 (8.4)
Common adverse event‡						
Nasopharyngitis	8 (8.1)	5 (10.6)	59 (9.0)	42 (12.8)	79 (10.7)	40 (10.9)
Myalgia	11 (11.1)	6 (12.8)	43 (6.6)	22 (6.7)	35 (4.8)	17 (4.6)
Urinary tract infection	11 (11.1)	4 (8.5)	27 (4.1)	21 (6.4)	33 (4.5)	22 (6.0)
Pain in extremity	8 (8.1)	1 (2.1)	23 (3.5)	8 (2.4)	19 (2.6)	7 (1.9)
Dizziness	5 (5.1)	3 (6.4)	30 (4.6)	16 (4.9)	30 (4.1)	12 (3.3)
Arthralgia	5 (5.1)	1 (2.1)	25 (3.8)§	23 (7.0)§	35 (4.8)	20 (5.4)
Upper respiratory tract infection	2 (2.0)	1 (2.1)	20 (3.1)	9 (2.8)	50 (6.8)	21 (5.7)
Fatigue	5 (5.1)	3 (6.4)	17 (2.6)§	17 (5.2)§	16 (2.2)	5 (1.4)

* P values were calculated for the comparison of event frequencies in the bempedoic acid group and the placebo group for each event and statin-intensity category with the use of a two-sided Fisher's exact test. P values were calculated without adjustment for multiple comparisons and are provided for descriptive purposes only. In post hoc analyses, there were no significant between-group differences with the exception of arthralgia and fatigue in the moderate-intensity category.

† Exact terms that were used to categorize muscle-related adverse events were the following: muscle spasms, myalgia, muscular weakness, increase in myoglobin blood level, presence of myoglobin in blood, presence of myoglobin in urine, myoglobinemia, myoglobinuria, myopathy, toxic myopathy, muscle necrosis, necrotizing myositis, pain in extremity, and rhabdomyolysis.

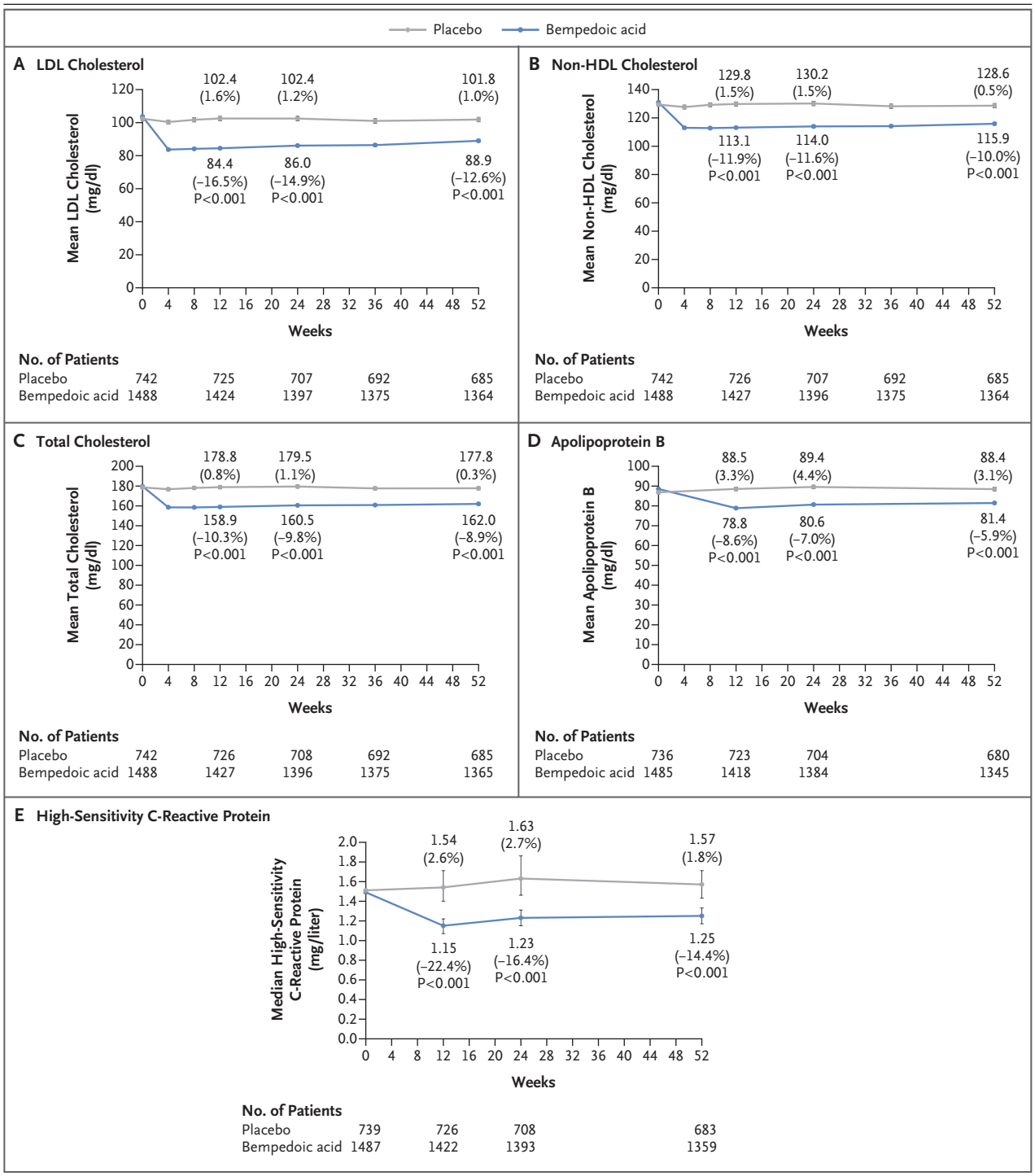
‡ Common adverse events during the intervention period were those reported in at least 6% of the patients in any statin-intensity subgroup of either trial group.

§ P=0.04 for the comparison between the bempedoic acid group and the placebo group.

Figure 1 (facing page). Efficacy Measures over the 52-Week Trial (Intention-to-Treat Population).

Means with standard errors are shown for the levels of low-density lipoprotein (LDL) cholesterol (Panel A), non–high-density lipoprotein (non-HDL) cholesterol (Panel B), total cholesterol (Panel C), and apolipoprotein B (Panel D). Data points with values listed indicate efficacy end points. Lipid concentrations were also measured at weeks 4, 8, and 36 (not efficacy end points, so no values are shown for these time points). To convert values for cholesterol to millimoles per liter, multiply by 0.02586. The percentage changes from baseline to week 12 (for all variables) and to week 24 (for the LDL cholesterol level) were analyzed with the use of analysis of covariance, with trial group and randomization strata as factors and baseline lipid value as a covariate. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen. At week 24 (for all variables other than the LDL cholesterol level) and at week 52 (for all variables), the percentage change was based on observed data. Because these data points were not part of the hierarchical analysis, P values (which are for the comparison of bempedoic acid with placebo) are considered to be descriptive. For the levels of LDL cholesterol, non-HDL cholesterol, and total cholesterol, baseline was defined as the mean of the values at screening and before receipt of the dose on trial day 1; for the apolipoprotein B level, baseline was defined as the last value before receipt of the first dose of trial agent. Median values are shown for the level of high-sensitivity C-reactive protein, and I bars indicate 95% confidence intervals (Panel E). The percentage change from baseline was analyzed with the use of a nonparametric approach, and P values are from the Wilcoxon rank-sum test. For the high-sensitivity C-reactive protein level, baseline was defined as the last value before the receipt of the first dose of trial agent. All the analyses of the high-sensitivity C-reactive protein level were based on observed data.

of background lipid-lowering therapy or across major subgroups, with the exception of there being a greater magnitude of effect with bempedoic acid therapy than with placebo among women than among men (Fig. 2, and Fig. S6 in the Supplementary Appendix). Post hoc analysis showed that changes after randomization in the use of adjunctive lipid-lowering therapy



(including PCSK9 inhibitors prescribed to five patients) did not appreciably affect the reduction in the LDL cholesterol level with bempedoic acid.

DISCUSSION

The present trial provides substantial evidence that bempedoic acid therapy as an adjunct to

Subgroup	Bempedoic Acid	Placebo	Least-Squares Mean Difference (95% CI)	P Value for Interaction
	no. of patients		*percentage points*	
Sex				0.03
Male	1058	519	−17.4 (−19.4 to −15.4)	
Female	336	206	−22.3 (−26.9 to −17.7)	
Race				0.82
White	1363	700	−18.7 (−20.7 to −16.8)	
Other	61	25	−20.0 (−34.0 to −6.1)	
Age <65 yr or ≥65 yr				0.71
<65 yr	576	260	−18.3 (−21.6 to −15.0)	
≥65 yr	848	465	−19.0 (−21.4 to −16.6)	
Age <75 yr or ≥75 yr				0.87
<75 yr	1182	590	−18.8 (−21.0 to −16.6)	
≥75 yr	242	135	−18.4 (−22.7 to −14.1)	
Cardiovascular disease risk category				
Atherosclerotic cardiovascular disease				0.43
Yes	1388	710	−18.6 (−20.6 to −16.7)	
No	36	15	−24.8 (−47.1 to −2.6)	
Heterozygous familial hypercholesterolemia				0.68
Yes	54	23	−20.6 (−35.7 to −5.4)	
No	1370	702	−18.7 (−20.6 to −16.7)	
Background lipid-lowering therapy				
Intensity of statin therapy				0.18
Low or moderate	706	362	−20.0 (−22.8 to −17.3)	
High	718	363	−17.5 (−20.2 to −14.7)	
Ezetimibe				0.57
Yes	112	53	−15.8 (−23.5 to −8.2)	
No	1312	672	−18.9 (−20.9 to −16.9)	
Fibrate				0.32
Yes	51	25	−23.8 (−34.1 to −13.5)	
No	1373	700	−18.5 (−20.5 to −16.6)	
Baseline LDL cholesterol				0.85
≥100 mg/dl	631	303	−18.8 (−21.5 to −16.1)	
<100 mg/dl	793	422	−18.5 (−21.3 to −15.7)	
History of diabetes				0.82
Yes	405	207	−19.1 (−22.7 to −15.5)	
No	1019	518	−18.6 (−20.9 to −16.3)	
Body–mass index				0.14
≥30	597	290	−20.1 (−24.9 to −15.2)	
25 to <30	624	320	−16.5 (−19.1 to −13.8)	
<25	201	114	−20.7 (−24.0 to −17.3)	
Geographic region				0.67
North America	480	252	−18.1 (−21.0 to −15.3)	
Europe	944	473	−19.1 (−21.6 to −16.5)	

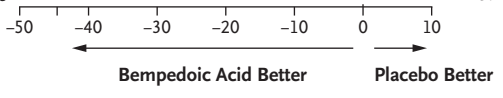


Figure 2. Subgroup Analysis of the Percentage Change from Baseline to Week 12 in the LDL Cholesterol Level (Intention-to-Treat Population).

Data are least-squares mean differences with 95% confidence intervals. The percentage change from baseline was analyzed with the use of analysis of covariance. All the analyses were based on observed data. For the LDL cholesterol level, baseline was defined as the mean of the values at screening and before receipt of the dose on trial day 1. Race was reported by the patient. The body-mass index is the weight in kilograms divided by the square of the height in meters.

guideline-based statin regimens appeared to have an acceptable safety profile.[2,12] Although the percentage of patients who discontinued the trial agent because of an adverse event was higher in the bempedoic acid group than in the placebo group, the difference in frequency did not appear to be driven by any single MedDRA system-organ class or preferred term. Gout occurred more frequently in the bempedoic acid group than in the placebo group. Bempedoic acid is known to be associated with modest elevations in the uric acid level; the putative mechanism is competition between the bempedoic acid glucuronide metabolite and uric acid for the same renal transporters that are involved in the excretion of these compounds. Observed decreases in the estimated glomerular filtration rate, for which the calculation depends on serum creatinine levels, are potentially also related to renal-transporter competition. The results regarding the secondary end point of efficacy were consistent, regardless of the intensity of background statin therapy or the use of additional background lipid-lowering therapy. Adverse events seemed random, with no graded relationship to the intensity of background statin therapy. The incidence of new-onset diabetes or worsening of diabetes was lower in the bempedoic acid group than in the placebo group, although the number of events was low, which makes it difficult to draw specific conclusions with our exploratory analyses.

When added to mostly moderate-intensity or high-intensity statin therapy in this predominantly white trial population, treatment with bempedoic acid reduced the levels of LDL cholesterol, non-HDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein significantly, as compared with placebo, from baseline to week 12. The magnitude of these reductions was similar to reductions that have been reported when ezetimibe was added to statins.[13,14] Favorable improvements in these lipid and biomarker levels were observed through week 52, although these favorable lipid effects were greater at week 12 — a phenomenon that is not uncommon in many lipid-lowering studies and is often referred to as "trial fatigue." The efficacy comparisons in the intention-to-treat and on-treatment analyses support our assertion.

Although statins and bempedoic acid work through the same cholesterol synthesis pathway, the additional reduction in the LDL cholesterol level with bempedoic acid therapy when it was added to moderate-intensity statin therapy is greater than the 6% reduction that has been quoted in the literature with doubling the dose of a statin.[15] Moreover, in our trial, the percentages of patients who discontinued the intervention owing to muscle-related adverse events were low in the two groups, myalgia and muscular weakness occurred at nearly equal frequency in the two groups, and muscle symptoms that have generally been associated with statin treatment were not further exaggerated by bempedoic acid therapy. Because muscle cells do not express very-long-chain acyl-CoA synthetase 1 (the enzyme required to activate bempedoic acid through conversion to its CoA conjugate),[6] treatment with bempedoic acid would be unlikely to cause adverse effects in skeletal muscle.

A greater number of deaths occurred in the bempedoic acid group than in the placebo group. The deaths from cancer generally occurred early in the course of the trial, a finding that probably represents preexisting cancers. No patterns or imbalances in nonfatal neoplasms were observed in our trial, and nonclinical data have not shown evidence of such neoplasms with bempedoic acid treatment to date (unpublished data). Hence, the observed imbalances in deaths from cancer are likely to be a chance finding. No significant between-group differences were observed in the incidence of cardiovascular events or mortality. A mendelian randomization study modeling the effects of lifelong lowering of ATP citrate lyase levels, the results of which are reported in this issue of the *Journal*,[16] suggests an association with a lower risk of cardiovascular events and no excess risk of cancer. Safety data with longer-term exposure are being assessed in a long-term, open-label extension of the present trial and in an ongoing cardiovascular-outcomes study.

In conclusion, in a 52-week trial, treatment with bempedoic acid added to maximally tolerated statin therapy did not lead to a higher over-

all incidence of adverse events than placebo and led to significantly lower LDL cholesterol levels.

Supported by Esperion Therapeutics and the NIHR Imperial Biomedical Research Centre.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the trial-site staff and the patients who participated in the trial; the staff of ICON Clinical Research for oversight of randomization of the patients, clinical laboratory services, statistical analyses, clinical monitoring, data management, and clinical programming; and Crystal Murcia, Ph.D., and Lamara D. Shrode, Ph.D., C.M.P.P., of JB Ashtin, for assistance in implementing revisions to an earlier version of the manuscript on the basis of the authors' input and direction.

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