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Bempedoic acid safety analysis: Pooled data from four phase 3 clinical trials

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Abstract

Background: An ongoing need exists for safe and effective lipid-lowering therapies (LLTs) for patients unable to achieve desired lipid levels with current treatment options.

Objective: Describe the safety profile of bempedoic acid, an oral, first-in-class, adenosine triphosphate (ATP)-citrate lyase inhibitor that significantly reduces low-density-lipoprotein cholesterol (LDL-C) levels by 17.4%–28.5% vs placebo.

Methods: This was a pooled analysis of four phase 3, randomized (2:1), double-blind, placebo-controlled studies in patients with hypercholesterolemia who required additional LDL-C lowering, despite stable maximally-tolerated LLT. Patients received bempedoic acid 180 mg (n=2424) or placebo (n=1197) once daily for 12 to 52 weeks. Assessments included treatment-emergent adverse events (TEAEs) and clinical laboratory tests.

Results: Of 3621 patients (median drug exposure: 363 days), exposure-adjusted TEAE rates were 87.1/100 and 82.9/100 person-years (PY) for bempedoic acid vs placebo, respectively. No single TEAE influenced the difference in rates. TEAEs leading to discontinuation occurred at rates of 13.4/100 and 8.9/100 PY for bempedoic acid vs placebo, with the most common cause being myalgia, which occurred less frequently with bempedoic acid vs placebo (1.5/100 vs 2.0/100 PY). Rates of myalgia and muscle weakness were comparable vs placebo. Bempedoic acid was associated with mild increases in blood urea nitrogen, creatinine, and uric acid, and decreases in hemoglobin. These laboratory abnormalities were apparent by week 4, stable over time, and reversible after treatment cessation. Gout incidence was 1.6/100 vs 0.5/100 PY in the bempedoic acid vs placebo groups. New-onset diabetes/hyperglycemia occurred less frequently with bempedoic acid vs placebo (4.7/100 vs 6.4/100 PY). The safety profile was consistent across subgroups.

Conclusions: Bempedoic acid is generally safe and well tolerated among patients with hypercholesterolemia who require additional LLT.

Keywords: ATP-citrate lyase inhibitor, hypercholesterolemia, low-density lipoprotein cholesterol, statins

Introduction

Clinical trial evidence supports reducing low-density lipoprotein cholesterol (LDL-C) levels as a strategy to decrease cardiovascular disease (CVD).[1,2] Prominent in the armamentarium for LDL-C reduction are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), whose safe and effective reduction of LDL-C and CVD events has secured their standard-of-care status.[3,4] However, a considerable proportion of patients fail to attain optimal lipid levels while receiving statin therapy with or without other nonstatin lipid-lowering therapies (LLTs).[5,6] This is particularly notable among patients at high risk for CVD, such as individuals with preexisting atherosclerotic CVD (ASCVD) or familial hypercholesterolemia, particularly when combined with multiple CVD risk factors.[7,8] Accentuating this challenge are statin-associated muscle symptoms, new-onset diabetes, or other side effects that make some patients unable to take statins in high enough doses to achieve risk-based LDL-C goals.[8-10]

Bempedoic acid (Esperion Therapeutics, Inc., Ann Arbor, MI, USA) is a first-in-class inhibitor of adenosine triphosphate (ATP)–citrate lyase, an enzyme two steps upstream of HMG-CoA reductase in the cholesterol synthesis pathway. As with statins, decreased hepatic cholesterol production upregulates LDL receptor expression, enhances clearance of circulating LDL-C, and thus lowers LDL-C levels in blood.[11] Unlike statins, bempedoic acid is not active in skeletal muscle and most other non-hepatic tissues due to absence of the enzyme very long-chain acyl-CoA synthetase-1 (ACSVL1), which is required to convert bempedoic acid to its active form.[11] Bempedoic acid is approved by both the US Food and Drug Administration and the European Medicines Agency for the treatment of hypercholesterolemia as its own entity and as a fixed-dose combination therapy with ezetimibe.

For any new agent, particularly one representing a novel therapeutic class, it is important to establish efficacy and define the safety/tolerability profile. Pooled analyses of data from phase 3 clinical trials[12-15] affirm significant LDL-C lowering with bempedoic acid vs placebo, including an ~18% lowering of LDL-C levels in high cardiovascular risk patients when added to maximally tolerated background statin therapy (with or without other LLTs) and an ~25% lowering of LDL-C levels in patients who were statin intolerant.[16] This report describes a detailed assessment of safety, based on pooled patient-level safety data from phase 3 bempedoic acid clinical trials.

Methods

Patients and studies

Patient-level data were pooled from four phase 3, double-blind, placebo-controlled clinical trials (N = 3621) wherein patients were randomized 2:1 to receive treatment with oral bempedoic acid 180 mg (n = 2424) or placebo (n = 1197) once daily (Fig. 1).[12-15] Patients qualified for study entry if they required additional LDL-C lowering despite ongoing maximally tolerated LLT. The CLEAR Harmony[13] (NCT02666664) and CLEAR Wisdom[15] (NCT02991118) studies enrolled patients at high risk for CVD (presence of ASCVD and/or heterozygous familial hypercholesterolemia [HeFH]) who were receiving stable background, maximally tolerated statin therapy with or without additional LLT. The CLEAR Tranquility[12] (NCT03001076) and CLEAR Serenity[14] (NCT02988115) studies enrolled patients with a history of statin intolerance. Patients could be enrolled in these latter two studies if they were treated with a maximally tolerated dose of no more than low-dose statin (lowest approved starting dose of statin [CLEAR Tranquility]) or very-low-dose statin (average daily dose less than the lowest approved starting dose of statin, as might occur with low dose statin therapy less than daily administration [CLEAR Serenity]). In CLEAR Tranquility, all patients were also on background ezetimibe 10 mg once daily.

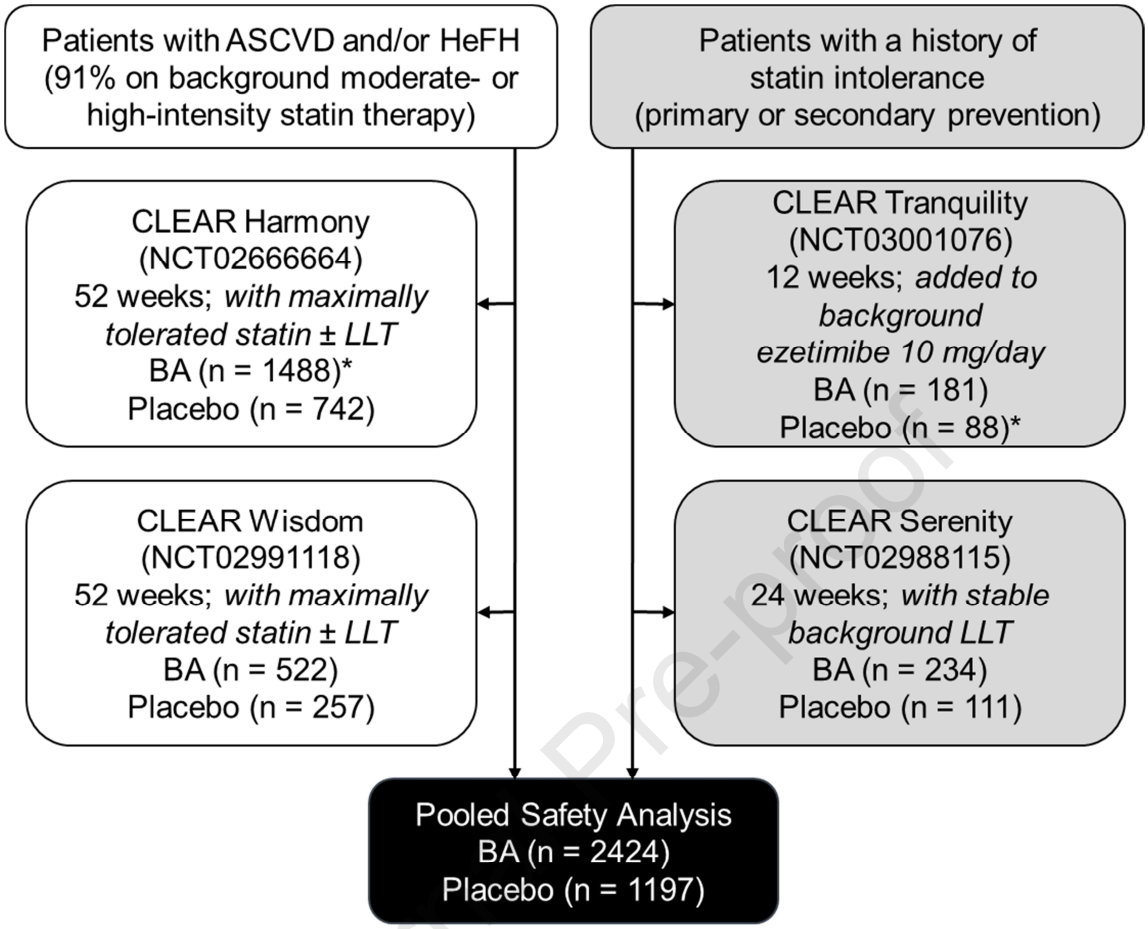

Figure 1 Studies included in the pooled analysis. ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy. *Two patients (one taking bempedoic acid and one taking placebo) did not receive any dose of study drug and were excluded from the safety analysis population.

The clinical trials described herein were conducted in accord with the ethical principles established by the Declaration of Helsinki and Good Clinical Practice guidelines. Study protocols were approved by local institutional review boards/independent ethics committees,

and all patients underwent the informed consent process and provided written informed consent.

Safety assessments

Safety was assessed through the continuous monitoring of treatment-emergent adverse events (TEAEs) via medical history, medical records, vital sign measurements, physical examinations, clinical laboratory results, and electrocardiograph readings. TEAEs included events that began or worsened in severity on or after the first dose through 30 days after the last dose of study drug. Reported TEAEs were coded according to Medical Dictionary of Regulatory Activities (MedDRA), version 20.1, preferred terms and classified by MedDRA System Organ Class designations.

TEAEs of special interest were identified based on (1) nonclinical or previous clinical findings for bempedoic acid; (2) known effects associated with statins or other LLTs; and/or (3) events related to the therapeutic area. These prespecified TEAEs of special interest included glycemic events (hypoglycemia, new-onset/worsening diabetes), metabolic acidosis, hepatic events, muscular safety events, neurologic/neurocognitive events, renal events (including increases in creatinine levels), increases in uric acid levels, decreases in hemoglobin levels, and cardiovascular events (see footnote of Table 3 for the preferred terms that comprised each category of TEAEs of special interest). Cardiovascular events were adjudicated by a blinded independent expert committee and included major adverse cardiovascular events (MACE [ie, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization]) and non-MACE (noncardiovascular death, noncoronary arterial revascularization, and hospitalization for heart failure) endpoints.

Statistical analysis

The safety analysis population included all randomized patients who received at least one dose of study drug. To assess differences in safety findings related to risk status, length of therapy, and/or background statin intensity, subset analyses were performed for similarly designed trials. Patients from the 52-week CLEAR Harmony and CLEAR Wisdom trials formed the ASCVD/HeFH on statins pool, and patients from CLEAR Tranquility and CLEAR Serenity trials comprised the statin-intolerant pool.

Exposure-adjusted incidence rates are reported for TEAEs. Prespecified composite 3-, 4-, and 5-component MACE were assessed via Kaplan-Meier estimates for the overall safety population and the ASCVD/HeFH on statins pool. Hazard ratios (HRs) and 95% CIs for the composite MACE endpoints were calculated using a Cox regression model. Given the small sample size; variance in the duration of treatment; small duration of exposure relative to the sample size; concerns of errors of multiplicity; and absence of a protocol-specified, a priori intention to apply statistical models to safety findings, *P* values of significance were not applied to MACE values, and non-MACE safety analyses were represented by descriptive statistics.

Results

Patients

A total of 3621 patients were included in the analysis (Fig. 1). Overall median study drug exposures were similar in the bempedoic acid group (362 days) and placebo group (363 days). Patient demographics and baseline characteristics were comparable in the bempedoic acid and placebo groups (Table 1). The majority of patients (3035 of 3621 [83.8%]) were receiving background statin with or without other LLT, and the majority of patients (80.8%) had history of ASCVD.

Table 1 Patient demographics and baseline characteristics, safety analysis population

Parameter	Bempedoic Acid (n = 2424)	Placebo (n = 1197)
Age, years*	65.2 ± 9.3	66.0 ± 9.0
Male, % (n)	66.0 (1600)	65.1 (779)
Race, % (n)		
White	94.4 (2289)	94.4 (1130)
Black	3.8 (93)	3.9 (47)
Other	1.7 (42)	1.7 (20)
Hispanic or Latino, % (n)	5.1 (123)	4.7 (56)
History of diabetes, % (n)	28.0 (678)	28.1 (336)
History of hypertension, % (n)	77.6 (1880)	78.9 (944)
History of ASCVD, % (n)	85.8 (2081)	86.6 (1037)
Body mass index, kg/m^{2}*	29.8 ± 5.0	29.9 ± 5.1
eGFR category, % (n)		
≥90 mL/min/1.73 m^2	21.9 (530)	21.3 (255)
≥60 to <90 mL/min/1.73 m^2	63.2 (1532)	63.3 (758)
<60 mL/min/1.73 m^2	14.9 (362)	15.4 (184)
Baseline LDL-C, mg/dL*	114.3 ± 36.6	113.1 ± 36.5
Background LLT, % (n)		
Statin alone	70.2 (1702)	70.8 (847)
Statin plus other LLT	13.5 (328)	13.2 (158)
Other LLT alone	9.4 (229)	9.3 (111)
None	6.8 (165)	6.8 (81)

Statin intensity, % (n)[†]		
Low or very low	8.3 (201)	7.9 (94)
Moderate	33.4 (810)	33.8 (404)
High	42.0 (1019)	42.4 (507)
Baseline ezetimibe use, % (n)	15.1 (365)	14.9 (178)

ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.
[*]Data are means ± standard deviations.
[†]Does not include patients on no statins.

Treatment-emergent adverse events

Exposure-adjusted rates of TEAEs were 87.1/100 person-years (PY) and 82.9/100 PY in the bempedoic acid and placebo groups, respectively (Table 2). No individual TEAE was responsible for the difference in rates between treatment groups. The most common TEAEs overall (irrespective of causality) included nasopharyngitis (8.9/100 PY and 10.1/100 PY for the bempedoic acid and placebo groups, respectively), myalgia (5.8/100 PY and 6.0/100 PY), urinary tract infection (5.4/100 PY and 6.3/100 PY), and arthralgia (4.9/100 PY and 5.4/100 PY).

Table 2 Treatment-emergent adverse events and key safety laboratory parameters, safety analysis population

Parameter	Bempedoic Acid (n = 2424)	Placebo (n = 1197)
Overview of AEs, exposure-adjusted incidence per 100 person-years (n)		
Any AE	87.1 (1771)	82.9 (868)
Serious AE	16.8 (341)	15.2 (159)
AE related to study drug	28.7 (583)	23.2 (243)
Drug discontinuation due to an AE	13.4 (273)	8.9 (93)
Most common AEs leading to drug discontinuation, exposure-adjusted incidence per 100 person-years (n)[*]		
Myalgia	1.5 (31)	2.0 (21)
Muscle spasms	0.9 (18)	0.3 (3)
Headache	0.5 (11)	0.3 (3)
Diarrhea	0.5 (11)	<0.1 (1)
Pain in extremity	0.5 (10)	0

AE with a fatal outcome[†]	0.9 (19)	0.4 (4)
Fatal outcome, cardiac disorders SOC	0.4 (8)	0.2 (2)
Fatal outcome, other	0.5 (11)	0.2 (2)
Most common AEs, exposure-adjusted incidence per 100 person-years (n)[‡]		
Nasopharyngitis	8.9 (180)	10.1 (106)
Myalgia	5.8 (118)	6.0 (63)
Urinary tract infection	5.4 (110)	6.3 (66)
Arthralgia	4.9 (100)	5.4 (57)
Laboratory results, exposure-adjusted incidence per 100 person-years (n)		
Aminotransferase level elevation >3 × ULN[§]	0.8 (18)	0.3 (3)
Aminotransferase level elevation >5 × ULN[§]	0.3 (6)	0.2 (2)
Creatine kinase level elevation >5 × ULN[§]	0.4 (8)	0.2 (2)
Creatinine level, median (Q1, Q3) change at week 12, mg/dL	0.04 (–0.02, 0.10)[¶]	0.00 (–0.05, 0.05)[‖]
Uric acid level, median (Q1, Q3) change at week 12, mg/dL	0.80 (0.30, 1.40)[**]	0.00 (–0.50, 0.40)[‖]
Hemoglobin level, median (Q1, Q3) change at week 12, g/dL	–0.30 (–0.70, 0.10)[††]	0.10 (–0.40, 0.50)[‡‡]
Reduction of ≥2 g/dL and <LLN[§§]	4.9 (112)	2.0 (23)
Reduction of ≥3 g/dL and <LLN[§§]	1.5 (34)	1.1 (13)
Reduction of ≥5 g/dL and <LLN[§§]	0.2 (5)	0.2 (2)
Patients with hemoglobin <8 g/dL	<0.1 (1)	0

AE, adverse event; LLN, lower limit of normal; SOC, Medical Dictionary of Regulatory Activities (MedDRA), version 20.1, System Organ Class; ULN, upper limit of normal.
Treatment-emergent adverse event incidence is defined as the number of patients having an event that started in a certain period divided by the total person time (in 100 person-years) at risk during this period.
[*]Events with an exposure-adjusted incidence of ≥ 10 per 100 person-years in either treatment group.
[†]All fatal AEs were judged by the investigator and medical monitor as unrelated to treatment.
[‡]Events with an exposure-adjusted incidence of > 5 per 100 person-years in either treatment group.
[§]Patients with repeated and confirmed elevations in aminotransferase or creatine kinase levels.
[¶]n = 2326. [‖]n = 1168. [**]n = 2321. [††]n = 2317. [‡‡]n = 1161.
[§§]Patients with values below the LLN during the study whose values were normal at baseline.

TEAEs leading to treatment discontinuation occurred at a rate of 13.4/100 PY (bempedoic acid) and 8.9/100 PY (placebo). The difference in frequency was not caused by an excess incidence of any single System Organ Class or preferred term. The most common TEAE leading to discontinuation was myalgia, which occurred less frequently with bempedoic acid vs placebo (1.5/100 PY vs 2.0/100 PY). The TEAEs leading to discontinuation that occurred more often with bempedoic acid vs placebo included muscle spasms, headache, diarrhea, and pain in

extremity, none of which differed in occurrence rate by more than 0.6/100 PY between treatment groups.

No notable differences were observed in serious AEs between treatment groups. The most frequent serious TEAE was unstable angina (1.5/100 PY [bempedoic acid] and 1.7/100 PY [placebo]). No individual treatment-related serious TEAE occurred in more than one patient. A total of 23 TEAEs with a fatal outcome were reported, with exposure-adjusted rates of 0.9/100 PY (bempedoic acid) and 0.4/100 PY (placebo). Cardiac disorder TEAEs with a fatal outcome occurred at exposure-adjusted rates of 0.4/100 PY (bempedoic acid) and 0.2/100 PY (placebo). No single AE or AE category drove the difference in deaths between groups, and all fatal events were judged unrelated to study treatment by the investigator and sponsor medical monitor.

Adjudicated clinical events

Positively adjudicated clinical events, including both cardiovascular (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization) and noncardiovascular events (noncardiovascular death, noncoronary arterial revascularization, and hospitalization for heart failure), occurred at exposure-adjusted rates of 5.3/100 PY and 6.0/100 PY in the bempedoic acid and placebo groups, respectively (Supplemental Table 1). Lower composite 3-, 4-, and 5-component MACE rates were observed with bempedoic acid vs placebo (HR [95% CI], 0.85 [0.53, 1.37], 0.95 [0.68, 1.34], and 0.91 [0.66, 1.27], respectively).

Treatment-emergent adverse events of special interest

Based on nonclinical or previous clinical findings for bempedoic acid, known effects associated with statins or other LLTs, and/or events related to the therapeutic area, several TEAEs of

special interest were identified and prespecified in each study protocol for observation. The following sections detail these TEAEs of special interest.

Elevated liver enzymes

The rate of repeated and confirmed (2 consecutive incidences) elevations in aminotransferase levels >3 times the upper limit of normal (ULN) was 0.8/100 PY (bempedoic acid) and 0.3/100 PY (placebo) (Table 2). Aminotransferase level >5 × ULN was 0.3/100 PY vs 0.2/100 PY. Aminotransferase levels all returned to <3 × ULN, regardless of whether the patient continued or discontinued study treatment. No patient in the bempedoic acid group had total bilirubin levels >2 × ULN, and no patient in either treatment group met Hy's Law criteria. Investigator-reported TEAEs of elevations in hepatic enzyme levels occurred at rates of 3.3/100 PY (bempedoic acid) and 1.4/100 PY (placebo) (Table 3).

Table 3 Adverse Events of Special Interest

	Exposure-Adjusted Incidence per 100 Person-Years (n)	
Parameter	Bempedoic Acid (n = 2424)	Placebo (n = 1197)
Hypoglycemia	2.0 (41)	2.4 (25)
Metabolic acidosis	<0.1 (1)	0
New-onset diabetes/hyperglycemia*	4.7 (96)	6.4 (67)
Hepatic enzyme elevation†	3.3 (67)	1.4 (15)
Aspartate aminotransferase levels increased	1.5 (30)	0.3 (3)
Alanine aminotransferase levels increased	1.1 (23)	0.2 (2)
Muscular disorders‡	15.4 (312)	11.9 (125)
Myalgia	5.8 (118)	6.0 (63)
Muscle spasms	4.4 (89)	3.0 (31)
Pain in extremity	3.7 (75)	2.0 (21)
Blood creatine phosphokinase levels increased	2.3 (47)	1.5 (16)
Muscular weakness	0.6 (13)	0.7 (7)
Myositis	0.1 (3)	0

Neurocognitive disorders[§]	0.8 (16)	0.9 (9)
Renal and urinary disorders[¶]	1.9 (38)	1.0 (10)
Renal disorder investigations	1.6 (32)	0.5 (5)
Blood creatinine levels increased	0.9 (19)	0.4 (4)
Glomerular filtration rate decreased	0.8 (16)	<0.1 (1)
Blood urea levels increased	0.1 (3)	<0.1 (1)
Blood uric acid levels increased	2.5 (51)	0.6 (6)
Hyperuricemia	2.0 (40)	0.7 (7)
Gout	1.6 (33)	0.5 (5)
Anemia	3.0 (60)	1.8 (19)

SOC, Medical Dictionary of Regulatory Activities (MedDRA), version 20.1, System Organ Class.
Data are based on investigator-reported adverse events.
Treatment-emergent adverse event incidence is defined as the number of patients having an event that started in a certain period divided by the total person time (in 100 person-years) at risk during this period.
[*]Category included MedDRA preferred terms: blood glucose abnormal, blood glucose increased, diabetes mellitus, diabetes mellitus inadequate control, diabetic ketoacidosis, glucose tolerance impaired, glucose urine present, glycosuria, glycosylated hemoglobin increased, hyperglycemia, impaired fasting glucose, ketoacidosis, ketosuria, ketosis, type 2 diabetes mellitus, and urine ketone body present.
[†]Category included MedDRA preferred terms: aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase abnormal, aspartate aminotransferase increased, blood bilirubin abnormal, blood bilirubin increased, hepatic enzyme abnormal, hepatic enzyme increased, hypertransaminasemia, liver function test abnormal, liver function test increased, transaminases abnormal, and transaminases increased.
[‡]Category included MedDRA preferred terms: muscular weakness, muscle necrosis, muscle spasms, myalgia, myositis, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinemia, myoglobinuria, myopathy, myopathy toxic, necrotizing myositis, pain in extremity, rhabdomyolysis.
[§]Category included MedDRA preferred terms: cognitive disorder, confusional state, disorientation, memory impairment, and mental status changes.
[¶]Events included renal failure, renal impairment, and acute kidney injury. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² was a study exclusion criterion. No patients had eGFR <15 mL/min/1.73 m².

Muscular symptoms

The TEAEs of special interest related to muscular symptoms occurred at rates of 15.4/100 PY (bempedoic acid) compared with 11.9/100 PY (placebo) (Table 3). Skeletal muscle TEAEs commonly attributed to statins were reported at similar incidence rates between treatment groups (myalgia, 5.8/100 PY [bempedoic acid] vs 6.0/100 PY [placebo]; muscular weakness, 0.6/100 PY [bempedoic acid] vs 0.7/100 PY [placebo]). No cases of myopathy or rhabdomyolysis were reported for either treatment group. Investigator-reported myositis occurred in three patients (0.1/100 PY) in the bempedoic acid group (vs zero in the placebo group), all of whom were receiving background statin therapy (simvastatin 40 mg, atorvastatin

20 mg, or atorvastatin 80 mg). A similar number of patients experienced elevations in creatine kinase levels >5 × ULN in both treatment groups (Table 2).

Uric acid elevation and gout

Bempedoic acid was associated with small mean increases in uric acid levels (mean change at week 12, 0.82 mg/dL [bempedoic acid] vs –0.02 mg/dL [placebo]), which were apparent within the first 4 weeks of treatment, were stable over time, and were reversible after treatment cessation (Fig. 2). Changes in uric acid levels were not influenced by baseline renal function (Supplemental Table 2).

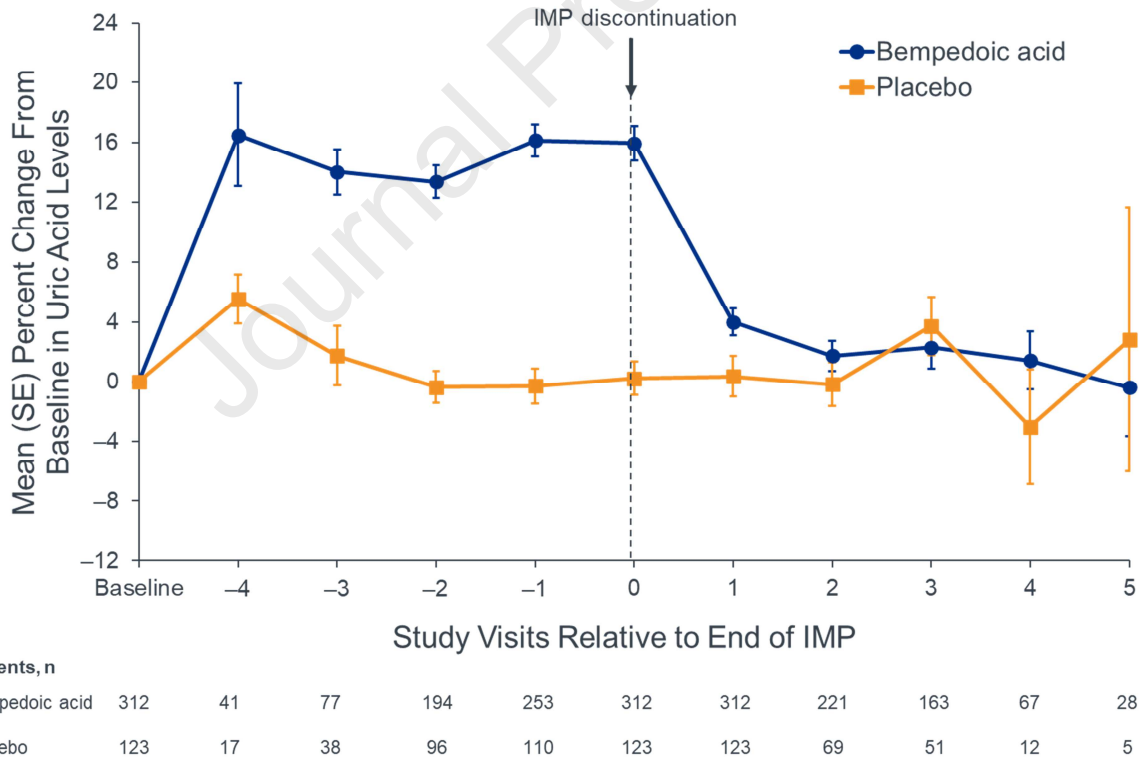

Figure 2 Change in uric acid before, during, and after treatment in the ASCVD/HeFH on statins pool. Data represent the subset of patients who underwent further assessments after discontinuing study treatment. Only patients with both pre- and post-IMP data are included.

Patients who discontinued study drug were encouraged to remain in the study and continue regularly scheduled study visits. There were no specific assigned time points for patients to return for assessment; in general, the timing of the study visit after discontinuation was based on the timing of discontinuation relative to the next scheduled visit. Values shown on the x-axis represent study visit time points. Time point 0 represents the last assessment prior to end of study drug treatment. Other time points are relative to time point 0 (eg, –2 means the second value prior to time 0 assessment). ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; IMP, investigational medicinal product.

The rate of gout was 1.6/100 PY (bempedoic acid) and 0.5/100 PY (placebo). A medical history of gout was present in 5.4% (196 of 3621) of the overall patient population. The incidence of gout was greater in patients who had a medical history of gout compared with those who had no medical history of gout (bempedoic acid, 11.0% vs 0.8%, respectively; placebo, 2.9% vs 0.3%, respectively) (Table 4). Further, among the subset of patients who had a history of gout, those with elevated uric acid levels at baseline had a greater incidence of gout than did those who had uric acid levels within normal limits (bempedoic acid, 23.1% vs 5.7%; placebo, 9.5% vs 0%). In patients without a history of gout, elevated uric acid levels at baseline were associated with a greater incidence of gout with bempedoic acid vs placebo (3.1% vs 0.4%, respectively), whereas uric acid levels within normal range at baseline were associated with a comparable incidence of gout for bempedoic acid and placebo (0.3% vs 0.2%, respectively). Among patients with a medical history of gout who experienced a TEAE of gout (bempedoic acid, n = 14; placebo, n = 2), most were male (bempedoic acid, n = 13; placebo, n = 1), some were receiving medication to treat gout when they had their first TEAE of gout (bempedoic acid, n = 6; placebo, n = 1), and few had a repeated incidence of gout during the studies (bempedoic acid, n = 4; placebo, n = 0). Of patients receiving gout medication at baseline, 7 of 20 in the bempedoic acid

group developed gout and 3 of 3 in the placebo group developed gout. Other potential clinical consequences of elevated uric acid levels, such as kidney stones, were infrequent (occurring in <1% of patients), and balanced between treatment groups.

Table 4 Incidence of gout by baseline uric acid levels and by medical history of gout

	TEAE of gout		No TEAE of gout	
Parameter	Bempedoic acid	Placebo	Bempedoic acid	Placebo
Patients with medical history of gout, % (n/total)	11.0 (14/127)	2.9 (2/69)	89.0 (113/127)	97.1 (67/69)
Uric acid levels at baseline, %* (n)				
≤ ULN	5.7 (5)	0	94.3 (83)	100 (48)
> ULN	23.1 (9)	9.5 (2)	76.9 (30)	90.5 (19)
Patients without medical history of gout, % (n/total)	0.8 (19/2297)	0.3 (3/1128)	99.2 (2278/2297)	99.7 (1125/1128)
Uric acid levels at baseline, %* (n)				
≤ ULN	0.3 (5)	0.2 (2)	99.7 (1841)	99.8 (899)
> ULN	3.1 (14)	0.4 (1)	96.9 (437)	99.6 (226)

TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
*Percentages are calculated based on the total number of patients with or without medical history of gout in each treatment group.

Other TEAEs of special interest

Rates of new-onset diabetes/hyperglycemia were 4.7/100 PY (bempedoic acid) and 6.4/100 PY (placebo). These rates were based on investigator reports of diabetes-related TEAEs (Table 3) as well as laboratory assessments of increased glucose levels ≥126 mg/dL or hemoglobin A1c levels ≥6.5%.

The proportions of patients who experienced other TEAEs of special interest, including hypoglycemia, metabolic acidosis, or neurocognitive disorders, were low and similar between the bempedoic acid and placebo groups (Table 3).

Other laboratory findings and related TEAEs of special interest

Bempedoic acid was associated with small increases in mean blood urea nitrogen (week 12, 1.7 mg/dL [bempedoic acid] vs 0.1 mg/dL [placebo]) and creatinine (week 12: 0.048 mg/dL [bempedoic acid] vs –0.002 mg/dL [placebo]) levels and small decreases in mean hemoglobin concentrations (Table 2). These findings were apparent within the first 4 weeks of treatment, were stable over time, and reversible after treatment cessation (Supplemental Figure). For the majority of patients, laboratory changes were not associated with clinical symptoms. Based on subgroup analyses of baseline renal function categories, no subgroup appears to have had significant impact on the changes in laboratory values. No meaningful clinical manifestations in the laboratory values were observed across baseline renal function categories. Renal AEs of special interest (ie, renal failure, renal impairment, acute kidney injury, increased blood creatinine levels, increased blood urea levels, and decreased eGFR), occurred in more patients treated with bempedoic acid, although the difference between groups was no more than 0.8/100 PY (Table 3).

Reductions in hemoglobin of ≥2 g/dL from baseline that resulted in values below the lower limit of normal were more frequent with bempedoic acid vs placebo, but the incidence was low in both groups (4.9/100 PY vs 2.0/100 PY, respectively; Table 2). Reductions in hemoglobin levels of ≥3 g/dL and below the lower limit of normal were generally balanced between the two treatment groups (1.5/100 PY [bempedoic acid] vs 1.1/100 PY [placebo]). One patient treated with bempedoic acid (vs no patients with placebo) developed clinically defined anemia (<8 mg/dL). This patient had a history of chronic recurrent iron deficiency anemia and was treated with a blood transfusion on hospitalization for severe anemia; the investigator did not consider the anemia to be related to bempedoic acid and the patient restarted bempedoic acid treatment after hemoglobin levels returned to normal range. Anemia reported as an AE occurred

at rates of 3.0/100 PY (bempedoic acid) and 1.8/100 PY (placebo) (Table 3). Small changes in hematocrit and erythrocyte levels were observed during the study; these changes were to a similar degree as seen with hemoglobin, with a mean change from baseline at week 4 of –1.1% (bempedoic acid) vs 0.5% (placebo) in hematocrit levels and –1.8% (bempedoic acid) vs –0.01% (placebo) in erythrocytes. The maximum mean percentage increase in platelet levels was observed for bempedoic acid (11.0%) vs placebo (4.0%). No clinically meaningful changes were found in mean corpuscular hemoglobin, mean corpuscular volume, or lactate dehydrogenase. No other changes in hematological measures occurred.

Other adverse events: tendon rupture

The overall incidence of the AE term, tendon rupture, was low, occurring in six patients (0.3/100 PY) in the bempedoic acid group and no cases in the placebo group. These reports of tendon rupture are from CLEAR Harmony and CLEAR Wisdom trials, as no incidence of tendon rupture was reported in the CLEAR Serenity or CLEAR Tranquility trials. Although not a prespecified TEAE of special interest, the US Food and Drug Administration conducted a separate analysis of the data and identified 10 cases of what they considered to be tendon rupture or injury (Supplemental Table 3)[17]; of these, six patients had an AE term of tendon rupture, three patients had rotator cuff syndrome, and one patient had tendon injury (confirmed by the investigator to not be a rupture). The majority of patients with tendon rupture had sustained injury in the setting of trauma or other mechanical stress and/or had a medical history of tendon rupture or injury. Beyond hypercholesterolemia present in all patients, additional risk factors present for tendon rupture included male sex (n = 9), diabetes (n = 4), renal impairment (n = 1), and statin use (n = 10).

Patient pools and subgroups

Safety assessments were also analyzed separately for patients in the ASCVD/HeFH on statins and statin-intolerant pools. Demographic and baseline characteristics were generally consistent with those of the overall analysis population.[16] The statin-intolerant pool included a greater proportion of women (58% vs 29%) and was more racially/ethnically diverse compared with the ASCVD/HeFH on statins pool, in which 97% of patients had preexisting ASCVD.

Safety measures in the two patient pools followed the trends observed for the overall population (Supplemental Table 4). Overall TEAE rates were higher in the statin-intolerant pool in both treatment groups. Rates of muscle-related TEAEs were not elevated with bempedoic acid treatment relative to placebo in the statin-intolerant pool. Among patients in the ASCVD/HeFH on statins pool, the incidences of myalgia and muscle weakness were similar in the bempedoic acid and placebo groups overall and in the subgroups of patients who received moderate- or high-intensity background statin therapy (data not shown).

Discussion

This analysis reports combined safety data from four phase 3 clinical trials encompassing more than 3600 patients (>3000 from 52-week studies). The pooled nature of the analysis using individual patient data provides insight into the safety of bempedoic acid beyond currently published data and systematic reviews/meta-analyses that use summary information[18-22], revealing a consistent profile across clinical trials and patient subgroups. Background LLT, which was used by the majority of patients, had no demonstrable effect on the safety or tolerability of bempedoic acid.

Several safety considerations (TEAEs of special interest) were identified a priori for additional scrutiny based on preclinical observations, experiences from prior clinical trials of other LLTs, and/or particular relevance to the disease state. Among these were muscle-related symptoms, the most common symptoms associated with statin intolerance. Bempedoic acid and statins both inhibit cholesterol synthesis enzymes, namely ATP citrate lyase and HMG-CoA reductase, respectively. Although the mechanism underlying statin-associated muscle symptoms is unclear, it was hypothesized that lack of bempedoic acid activation in skeletal muscle would limit such symptoms from occurring with bempedoic acid.[11] In our analysis, myalgia and muscle weakness were comparable in the bempedoic acid and placebo groups. Parity between treatments was observed even among patients who were receiving background high-intensity statin therapy and patients with a history of statin intolerance. No cases of rhabdomyolysis occurred in these studies.

Administration of bempedoic acid resulted in slight elevations in alanine aminotransferase and aspartate aminotransferase in these studies. The incidence of repeated and confirmed elevations in alanine aminotransferase and/or aspartate aminotransferase is within the range of

aminotransaminase elevations >3 × ULN reported for statins (0.2%–2.3% atorvastatin,[23] 1.1% rosuvastatin,[24] 0.9%–2.1% simvastatin[25]) and for ezetimibe (0.5%)[26]. The incidence of repeated and confirmed aminotransferase elevations >5 × ULN was comparable between treatment groups. The incidence of prespecified TEAEs of special interest within hepatic events was low. These results appear to be consistent with prior clinical experience with statins and were not associated with any other AEs. No patient in the bempedoic acid group met the criteria for potential Hy's Law.

Statins are associated with a small risk of incident diabetes, particularly with high-intensity statins and in patients at risk for diabetes.[27,28] In this pooled analysis, new-onset diabetes and worsening of diabetes occurred less frequently with bempedoic acid vs placebo. Other analyses have reported numerically lower hemoglobin A1c levels in patients with diabetes who received bempedoic acid vs placebo after 12 weeks of treatment.[29] A separate analysis of the effect of bempedoic acid on glycemic parameters in patients who have diabetes or prediabetes is ongoing.

Laboratory assessments revealed mild increases in creatinine, blood urea nitrogen, and uric acid levels in the bempedoic acid group that returned to baseline levels after discontinuation of treatment. The observed increases in creatinine and uric acid levels appear to be primarily due to an effect of bempedoic acid on organic anion transporter 2, a renal transporter involved in excretion of creatinine and uric acid.[30,31] In preclinical studies, bempedoic acid demonstrated inhibitory activity toward organic anion transporter 2, including specific effects on uric acid and creatinine levels as substrates (unpublished data). The mechanism for the mild increases in blood urea nitrogen levels is not known.

One of the unique aspects of this safety analysis of bempedoic acid was the assessment of the relationship between uric acid levels and gout, which may provide clinicians practical clinical guidance. Firstly, the overall rate of gout in this pooled analysis was low (bempedoic acid, 1.6/100 PY and placebo, 0.5/100 PY). Secondly, patients who had a medical history of gout had a greater chance of gout compared with those patients who had no medical history of gout (bempedoic acid, 11.0% vs 0.8%, respectively; placebo, 2.9% vs 0.3%, respectively). Thirdly, patients who had a history of gout and elevated uric acid levels at baseline had a greater incidence of gout than did those who had uric acid levels within normal limits (bempedoic acid, 23.1% vs 5.7%; placebo, 9.5% vs 0%). Fourthly, in patients without a history of gout, elevated uric acid levels at baseline were associated with a greater incidence of gout with bempedoic acid vs placebo (3.1% vs 0.4%, respectively). Finally, if the uric acid levels were within normal range at baseline in patients without a history of gout, then the onset of gout was similar between patients taking bempedoic acid and placebo (0.3% vs 0.2%, respectively).

Mild reversible reductions in hemoglobin levels were also associated with bempedoic acid. One patient in the bempedoic acid group experienced a hemoglobin level <8 mg/dL; however, the investigator did not consider this AE to be related to bempedoic acid and the patient continued bempedoic acid treatment after hemoglobin levels returned to normal range. The mechanism by which bempedoic acid may have an association with reduced hemoglobin levels is unknown. The adverse event of anemia was reported by a low proportion of patients in both groups (3.0% vs 1.8% for bempedoic acid and placebo, respectively), no qualitative changes existed in red blood cells (eg, mean corpuscular hemoglobin concentration), and no evidence supported plasma dilution as a potential cause.

In this pooled analysis, the frequency of tendon rupture was low (six of 2424 patients who received bempedoic acid), which was based on the MedDRA preferred term of “tendon rupture”,

unlike the terms used by the US Food and Drug Administration in a separate analysis (broader criteria included three cases of rotator cuff syndrome and one case of tendon injury). Hypercholesterolemia (particularly HeFH), is associated with an increased risk of tendon rupture.[32] Other risk factors for tendon rupture include statin use, diabetes, fluoroquinolone or systemic steroid use, renal failure, age over 60 years, male sex, and previous tendon disorders.[33-37] In this pooled analysis, all patients who developed tendon rupture had one or more of these potential risk factor(s) for tendon rupture (no patients who had tendon rupture were taking concomitant fluoroquinolone or systemic steroid medication) (Supplemental Table 3).

Limitations of this analysis include pooling of data from studies of varying duration that differed in patient enrollment criteria. Background LLT was also heterogeneous both within and among studies. However, the diversity of background treatment, and the variance in the duration of treatment might have applicability to patients commonly encountered in clinical practice. Because the majority of patients enrolled in the studies were white, the generalizability to underrepresented racial and ethnic groups is limited. The longest study duration was 52 weeks, which may limit any long-term safety conclusions; however, further insights into the long-term effects of bempedoic acid will come from the CLEAR Harmony open-label extension study (NCT03067441), in which 1462 patients who were eligible and chose to participate could achieve a total of up to 2.5 years of bempedoic acid treatment. Additional insights on the bempedoic acid safety profile will come from the ongoing ~14,000-patient, event-driven cardiovascular outcomes trial (CLEAR Outcomes; NCT02993406) conducted in patients with statin intolerance for an estimated average treatment duration of 3.5 years. The estimated study completion date for CLEAR Outcomes is 2022.

In summary, in this pooled analysis, bempedoic acid was generally well tolerated. Bempedoic acid was associated with small increases in creatinine and uric acid levels and greater incidence of gout, as well as infrequent decreases in hemoglobin levels. Elevations in other laboratory values were generally reversible and not considered related to treatment. The safety profile of bempedoic acid was consistent when used in conjunction with other LLTs (eg, statins and/or ezetimibe) and within different patient subgroups. Compared with placebo, bempedoic acid did not increase myalgia and muscle weakness to a clinically meaningful degree, even among a subset of patients with a history of statin intolerance. This pooled safety analysis revealed no cases of rhabdomyolysis. With its demonstrated efficacy and favorable safety profile, bempedoic acid may be a useful addition to the LLT armamentarium, especially among patients wherein safety and tolerability issues with other LLTs may be a concern.

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Data sharing statement

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedures.

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Author contributions

Harold E. Bays, Maciej Banach, Alberico L. Catapano, Ulrich Laufs, and Kausik K. Ray were all involved in the concept/design of the manuscript and data interpretation. P. Barton Duell, Lawrence A. Leiter, and G.B. John Mancini were involved in the data interpretation. LeAnne T. Bloedon, William J. Sasiela, and Christie M. Ballantyne were all involved in the concept/design of the manuscript, data acquisition, and data interpretation. Zhan Ye was involved in the concept/design, data acquisition, statistical analysis, and data interpretation. All authors critically reviewed the manuscript and approved the final version of the manuscript for submission.

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Highlights

- Bempedoic acid significantly lowered LDL-C in 4 phase 3 placebo-controlled trials
- Bempedoic acid had an adverse event profile similar to placebo
- Bempedoic acid was associated with increases in uric acid and incidence of gout
- New-onset diabetes/hyperglycemia incidence was lower with bempedoic acid vs placebo
- Bempedoic acid was generally well-tolerated with consistent safety in subgroups

Bempedoic acid safety analysis: Pooled data from four phase 3 clinical trials

SUPPLEMENTAL MATERIAL

Supplemental Table 1 Adjudicated clinical events, safety analysis population

Parameter	Exposure-adjusted incidence per 100 person-years (n)		Hazard Ratio (95% CI)
	Bempedoic Acid (n = 2424)	Placebo (n = 1197)	
Any positively adjudicated event	5.3 (120)	6.0 (68)	NC
Adjudicated MACE			
Cardiovascular death	0.4 (10)	0.3 (3)	NC
Nonfatal myocardial infarction	1.1 (26)	1.9 (22)	
Nonfatal stroke	0.5 (11)	0.4 (4)	
Hospitalization for unstable angina	1.3 (30)	1.3 (15)	
Coronary revascularization	2.9 (66)	3.5 (40)	
Other adjudicated non-MACE events			
Noncardiovascular death	0.2 (4)	<0.1 (1)	NC
Noncoronary arterial revascularization	0.5 (11)	1.1 (12)	
Hospitalization for heart failure	0.6 (14)	0.3 (3)	
3-component MACE[*]	2.0 (45)	2.4 (27)	0.85 (0.53, 1.37)
4-component MACE[†]	4.1 (93)	4.4 (50)	0.95 (0.68, 1.34)
5-component MACE[‡]	4.3 (98)	4.8 (55)	0.91 (0.66, 1.27)

Treatment-emergent adverse event incidence is defined as the number of patients having an event that started in a certain period divided by the total person time (in 100 person-years) at risk during this period.
MACE, major adverse cardiovascular events; NC, not calculated.
[*]3-component MACE was defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
[†]4-component MACE was defined as 3-component MACE events plus coronary revascularization.
[‡]5-component MACE was defined as 4-component MACE events plus hospitalization for unstable angina.

Supplemental Table 2 Summary of changes in uric acid by baseline eGFR category in the overall safety population

	Baseline eGFR					
	30 to <60 mL/min/1.73 m^2		60 to <90 mL/min/1.73 m^2		≥90 mL/min/1.73 m^2	
Uric acid values, mean (SD)	Bempedoic acid (n = 359)	Placebo (n = 183)	Bempedoic acid (n = 1532)	Placebo (n = 758)	Bempedoic acid (n = 530)	Placebo (n = 255)
Baseline, mg/dL	6.6 (1.5)	6.5 (1.5)	6.0 (1.4)	6.0 (1.3)	5.6 (1.3)	5.5 (1.3)
Week 4, % change	12.8 (17.3) (n = 347)	1.2 (11.2) (n = 181)	13.9 (15.0) (n = 1494)	0.3 (12.2) (n = 744)	13.8 (15.2) (n = 513)	2.2 (13.5) (n = 247)
Week 12, % change	15.0 (23.3) (n = 345)	–1.0 (13.8) (n = 177)	14.7 (16.0) (n = 1464)	0.02 (13.0) (n = 742)	14.9 (16.0) (n = 509)	3.8 (16.0) (n = 248)
Week 52, % change	13.7 (21.5) (n = 268)	1.2 (24.7) (n = 129)	13.1 (20.2) (n = 1168)	–0.04 (15.0) (n = 582)	13.9 (19.4) (n = 388)	1.9 (15.1) (n = 206)

eGFR, estimated glomerular filtration rate; SD, standard deviation.

Supplemental Table 3 Description of tendon rupture and injury cases among patients in the four phase 3 studies, as identified by the FDA

Sex	Age, y	Risk Factors* MH	Tr	DM	RI	SU	Verbatim term/ preferred term	Relevant MH or circumstances	Relevant concomitant medications	Onset day†
CLEAR Harmony										
Male	65	✓				✓	Biceps tendon tear left/ Tendon rupture	Past history of left rotator cuff pain years before entering study; bilateral tennis elbow 1983	Atorvastatin 40 mg/day; on for 1 year prior to event	106
							Left shoulder rotator cuff tear/ Rotator cuff syndrome			188
Male	52		✓			✓	Tendinus rupture shoulder right/ Tendon rupture	No relevant MH Rupture occurred when catching a TV that he dropped	Rosuvastatin 5 mg/week; on for 5 months prior to event	345
Male	70	✓		✓		✓	Tendon rupture of biceps/ Tendon rupture	Arthralgia of left shoulder joint reported 5 days prior to first dose	Atorvastatin 20 mg/day; on for 3.5 years prior to event	269
Male	63	✓		✓	✓	✓	Right rotator cuff tear/ Rotator cuff syndrome‡	Past history of torn knee ligament (right and left) months before entering study	Atorvastatin 40 mg/day; on for 6 months prior to event	128
Male	78	✓	✓	✓		✓	Right shoulder torn rotator cuff/ Rotator cuff syndrome‡	No relevant MH Tendon tear as the result of a work-related injury	Simvastatin 10 mg/day; on for 6 years prior to event	15
Male	63	✓				✓	Achilles tendon injury on both sides/ Tendon injury‡	No relevant MH No documentation of tendon tear or rupture	Mirtazapine 30mg PRN; on for 5 years prior to event Atorvastatin 40 mg/day; on for 2 years prior to event	106

CLEAR Wisdom										
Male	60		✓			✓	Tendon rupture right shoulder/ Tendon rupture	No relevant MH Tendon rupture was the direct result of a fall onto the right shoulder	Atorvastatin 40 mg/day; 9 years to 1.5 years prior to event Fluvastatin 20 mg/day; on for 1.5 years prior to event	126
Female	52			✓		✓	Rupture of right biceps/ Tendon rupture	No relevant MH	Atorvastatin 40 mg/day; on for 1.5 years prior to event	165
Male	60		✓			✓	Avulsive rupture of right bicep tendon enthesis/ Tendon rupture	No relevant MH Avulsion occurred while lifting weights	Rosuvastatin 40 mg/day; on for 3.5 years prior to event	65
Male	68	✓	✓			✓	Left tear of rotator cuff/ Rotator cuff syndrome‡	Two rotator cuff repairs years before entering the study. Never completely symptom free after prior procedures. Current tendon tear (confirmed rupture) occurred while lifting a heavy box from back seat of car with arm extended and sensed a tearing sensation reminiscent of his prior injury	Pravastatin 20 mg/day; 3 years to 1 year prior to event Betamethasone cream (topical) PRN; on for 10 years prior to event Triamcinolone cream (topical) PRN; on for 4 years prior to event	155

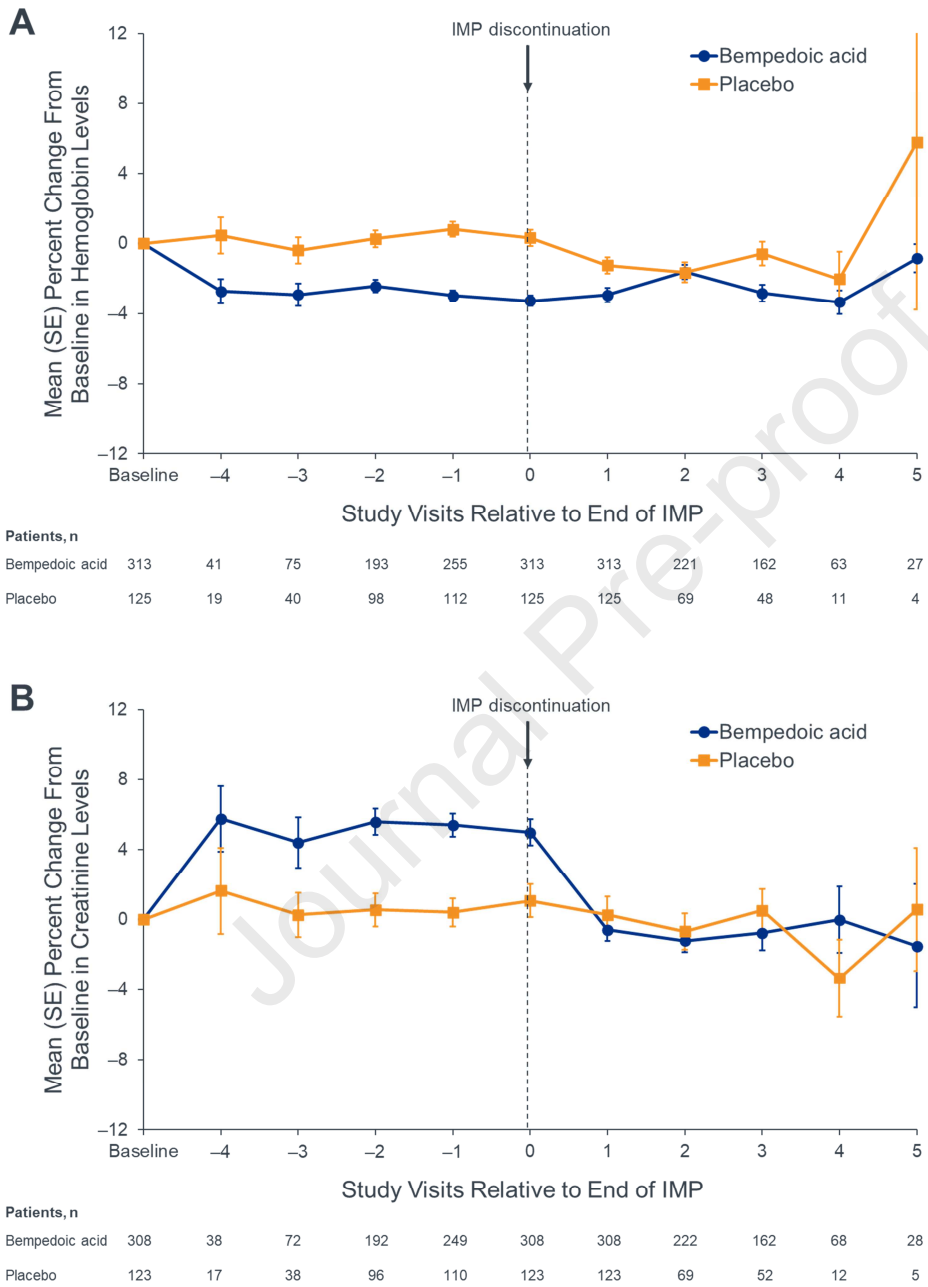
ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus (type 1 or type 2); HeFH, heterozygous familial hypercholesterolemia; MH, medical history of tendon rupture/injury; PRN, as needed; RI, renal impairment; SU, statin use; Tr, physical trauma; y, years.

*Risk factors for tendon rupture included prior medical history of tendon rupture or injury, physical trauma, diabetes mellitus (Type 1 or Type 2), renal impairment, and/or statin use. All patients also fulfill the risk factor of advanced age and having hyperlipidemia.

†Onset day is the day of TEAE occurrence relative to the first dose of bempedoic acid.

‡Denotes additional patients identified by the US Food and Drug Administration as having tendon rupture or injury (rotator cuff syndrome, n = 3; tendon injury, n = 1).

Supplemental Figure



Supplemental Figure. Changes in (A) hemoglobin and (B) creatinine levels before, during, and after treatment in the ASCVD/HeFH on statins pool. Data represent the subset of patients who underwent further assessments after discontinuing study treatment. Only patients with both pre- and post-IMP data are included. Patients who discontinued study drug were encouraged to

remain in the study and continue regularly scheduled study visits. There were no specific assigned time points for patients to return for assessment; in general, the timing of the study visit after discontinuation was based on the timing of discontinuation relative to the next scheduled visit. Values shown on the x-axis represent study visit time points. Time point 0 represents the last assessment prior to end of study drug treatment. Other time points are relative to time point 0 (eg, –2 means the second value prior to time 0 assessment). ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; IMP, investigational medicinal product.

Supplemental Table 4 Treatment-emergent adverse events and key safety laboratory parameters in the ASCVD/HeFH on statins and statin intolerant pools

	ASCVD/HeFH on statins		Statin intolerant	
Parameter	Bempedoic Acid (n = 2009)	Placebo (n = 999)	Bempedoic Acid (n = 415)	Placebo (n = 198)
Overview of AEs, exposure-adjusted incidence per 100 person-years (n)				
Any AE	82.2 (1533)	79.5 (766)	141.7 (238)	123.5 (102)
Serious AE	17.3 (322)	15.8 (152)	11.3 (19)	8.5 (7)
AE related to study drug	26.4 (493)	22.3 (215)	53.6 (90)	33.9 (28)
Drug discontinuation due to an AE	11.7 (219)	7.8 (75)	32.1 (54)	21.8 (18)
AE with a fatal outcome*	1.0 (19)	0.4 (4)	0	0
Fatal outcome, cardiac disorders SOC	0.4 (8)	0.2 (2)	0	0
Fatal outcome, other	0.6 (11)	0.2 (2)	0	0
Adverse events of special interest, exposure-adjusted incidence per 100 person-years (n)				
Hypoglycemia	2.1 (40)	2.6 (25)	0.6 (1)	0
Metabolic acidosis	<0.1 (1)	0	0	0
New-onset diabetes/hyperglycemia†	4.6 (85)	6.1 (59)	6.5 (11)	9.7 (8)
Hepatic enzyme elevation‡	2.7 (51)	1.6 (15)	9.5 (16)	0
Aspartate aminotransferase levels increased	1.4 (26)	0.3 (3)	2.4 (4)	0
Alanine aminotransferase levels increased	1.0 (19)	0.2 (2)	2.4 (4)	0

Muscular disorders				
Myalgia	5.6 (104)	5.5 (53)	8.3 (14)	12.1 (10)
Muscle spasms	3.9 (73)	2.4 (23)	9.5 (16)	9.7 (8)
Pain in extremity	3.3 (61)	1.8 (17)	8.3 (14)	4.8 (4)
Blood creatine phosphokinase levels increased	2.1 (39)	1.7 (16)	4.8 (8)	0
Muscular weakness	0.6 (11)	0.5 (5)	1.2 (2)	2.4 (2)
Myositis	0.2 (3)	0	0	0
Neurocognitive disorders[§]	0.8 (14)	0.8 (8)	1.2 (2)	1.2 (1)
Renal and urinary disorders[¶]	1.7 (32)	0.8 (8)	3.6 (6)	2.4 (2)
Investigations in renal disorders SOC	1.5 (28)	0.5 (5)	2.4 (4)	0
Blood creatinine levels increased	0.9 (16)	0.4 (4)	1.8 (3)	0
Glomerular filtration rate decreased	0.6 (12)	0.1 (1)	2.4 (4)	0
Blood urea levels increased	0.2 (3)	0.1 (1)	0	0
Blood uric acid levels increased	1.8 (33)	0.4 (4)	10.7 (18)	2.4 (2)
Hyperuricemia	2.0 (37)	0.7 (7)	1.8 (3)	0
Gout	1.6 (29)	0.4 (4)	2.4 (4)	1.2 (1)
Anemia	3.1 (57)	2.0 (19)	1.8 (3)	0
Laboratory results, exposure-adjusted incidence per 100 person-years (n)				
Aminotransferase level elevation >3 × ULN[‖]	0.6 (13)	0.3 (3)	2.8 (5)	0
Aminotransferase level elevation >5 × ULN[‖]	0.2 (4)	0.2 (2)	1.1 (2)	0
Creatine kinase level elevation >5 × ULN[‖]	0.3 (7)	0.2 (2)	0.6 (1)	0

Creatinine, median (Q1, Q3) change at week 12, mg/dL	0.04 (–0.02, 0.10)[**]	–0.01 (–0.05, 0.05)[††]	0.04 (–0.03, 0.11)[‡‡]	0.01 (–0.06, 0.06)[§§]
Uric acid levels, median (Q1, Q3) change at week 12, mg/dL	0.80 (0.30, 1.40)[¶¶]	0.00 (–0.40, 0.50)[††]	0.60 (0.10, 1.20)[‖‖]	–0.20 (–0.60, 0.40)[§§]
Hemoglobin levels, median (Q1, Q3) change at week 12, g/dL[g]	–0.30 (–0.70, 0.10)[***]	0.10 (–0.40, 0.50)[†††]	–0.40 (–0.80, 0.20)[‖‖]	–0.10 (–0.30, 0.50)[‡‡‡]
Reduction of ≥2 g/dL and < LLN[**]	4.9 (103)	2.2 (23)	5.0 (9)	0
Reduction of ≥3 g/dL and < LLN[**]	1.4 (29)	1.2 (13)	2.8 (5)	0
Reduction of ≥5 g/dL and < LLN[**]	0.1 (3)	0.2 (2)	1.1 (2)	0
Patients with hemoglobin <8 g/dL	<0.1 (1)	0	0	0

AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LLN, lower limit of normal; SOC, Medical Dictionary of Regulatory Activities (MedDRA), version 20.1, System Organ Class; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Exposure-adjusted TEAE incidence is defined as the number of patients having an event started in a certain period divided by the total person time (in 100 person-years) at risk during this period. Exposure-adjusted rates can be greater than 100 per 100 person-years.

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

[†]Category included MedDRA preferred terms: blood glucose abnormal, blood glucose increased, diabetes mellitus, diabetes mellitus inadequate control, diabetic ketoacidosis, glucose tolerance impaired, glucose urine present, glycosuria, glycosylated hemoglobin increased, hyperglycemia, impaired fasting glucose, ketoacidosis, ketosuria, ketosis, type 2 diabetes mellitus, and urine ketone body present.

[‡]Category included MedDRA preferred terms: aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase abnormal, aspartate aminotransferase increased, blood bilirubin abnormal, blood bilirubin increased, hepatic enzyme abnormal, hepatic enzyme increased, hypertransaminasemia, liver function test abnormal, liver function test increased, transaminases abnormal, and transaminases increased.

[§]Category included MedDRA preferred terms: cognitive disorder, confusional state, disorientation, memory impairment, and mental status changes.

[¶]Events included renal failure, renal impairment, and acute kidney injury. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² was a study exclusion criterion. No patients had eGFR <15 mL/min/1.73 m².

[‖]Patients with repeated and confirmed elevations in aminotransferase or creatine kinase levels.

[**]n = 1926. [††]n = 979. [‡‡]n = 400. [§§]n = 189. [¶¶]n = 1922. [‖‖]n = 399. [***]n = 1918. [†††]n = 971. [‡‡‡]n = 190.

Patients with values below the LLN during the study whose values were normal at baseline.