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Efficacy and safety of bempedoic acid in patients not receiving statins in phase 3 clinical trials

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KEYWORDS
Bempedoic acid;
Ezetimibe;
Low-density lipoprotein cholesterol;
Statin;
Statin-associated muscle symptoms (SAMS);
Statin intolerance

Abstract:

Background: Despite the high incidence of patients with statin tolerance problems, randomized evaluations of nonstatin oral treatment options for lowering of low-density lipoprotein cholesterol (LDL-C) in this population are sparse.

Objective: To assess the LDL-C lowering effect of bempedoic acid in patients not taking statins.

Methods: This was a pooled analysis of data from patients enrolled in four phase 3 bempedoic acid studies (12 to 52 weeks in duration) who were not taking concomitant statins (Phase 3 No Statin Cohort) and a phase 3 bempedoic acid plus ezetimibe fixed-dose combination study (BA+EZE FDC No Statin

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Cohort). The primary endpoint for all studies was the percent change from baseline to week 12 in LDL-C levels. Safety and tolerability were assessed by laboratory values and adverse events.

Results: In the Phase 3 No Statin Cohort, bempedoic acid (n = 394) lowered LDL-C levels at week 12 significantly more than placebo (n = 192; −26.5% [95% CI, −29.7%, −23.2%]; $P<0.001$). The fixed-dose combination of bempedoic acid with ezetimibe lowered LDL-C by 39.2% (95% CI, −51.7% to −26.7%; $P<0.001$). Muscle-related disorders occurred at a rate of 26.4 and 28.6 per 100 person-years with bempedoic acid and placebo, respectively.

Conclusions: In patients with hypercholesterolemia unable to take statins, bempedoic acid lowered LDL-C levels by a mean of 26.5% vs placebo and bempedoic acid + ezetimibe fixed-dose combination lowered LDL-C by 39.2%. The treatments were generally well tolerated, suggesting that bempedoic acid may be efficacious and well tolerated in this challenging-to-treat patient population.

Introduction

Statins are well established as the recommended first-line pharmacotherapy for treatment of hypercholesterolemia. This recommendation is based on observed reductions in cardiovascular events attributable to lowering low-density lipoprotein cholesterol (LDL-C), extensive clinical experience, and low cost.[1,2] However, in real-world studies up to 10-15% of patients are unable to tolerate a dose of statin required to sufficiently reduce LDL-C,[3-6] and a smaller proportion of patients are unable to tolerate any dose of statin therapy,[7,8] resulting in statin nonadherence, poor persistence, and increased LDL-C levels, ultimately leading to poor cardiovascular outcomes.[6,9-11]

Manifestations of side effects attributed to statin intolerance include muscle symptoms, typically myalgia, myopathy, and muscle weakness; less frequently, myositis and elevations in creatine kinase and, rarely, rhabdomyolysis.[12-14] Some statin-associated muscle symptoms may be the result of a "drucebo" effect (a combination of drug and nocebo) in which patients who know they are receiving a statin are more likely to attribute unrelated symptoms to the drug than patients who are blinded to treatment.[15,16] This theory is supported by similar rates of muscle symptoms (∼10%) or discontinuations due to muscle symptoms (∼1%) among patients randomized to receive either statins or placebo in some blinded clinical trials,[8] and by demonstrated nocebo/drucebo effect in n-of-one randomized, controlled trials.[16] By contrast, in a survey of > 10,000 statin-treated patients, 62% permanently discontinued statin due to side effects.[4] Others have reported that 7%–29% of patients treated with statins complain of muscle-related symptoms.[4,6] Although rare, and not necessarily caused by a statin, neurological symptoms, new-onset diabetes mellitus and temporary or persistent elevations in liver transaminase levels may occur with statin use, and may lead to a reduction of statin dose or discontinuation of statins altogether.[1,2,8] In patients who experience side effects attributed to statins, symptoms are sometimes very challenging to manage, requiring extra effort by healthcare providers and staff to work with patients to effectively treat elevated LDL-C levels (eg, switch to a different statin, lower statin dose, add additional non–lipid-lowering therapies). As a result, nonstatin therapies are needed to lower LDL-C levels to achieve risk-based goals in these patients.

Bempedoic acid (NEXLETOL®, Esperion Therapeutics, Inc) targets ATP-citrate lyase (ACL), an enzyme in the cholesterol synthesis pathway that is upstream from the statin target, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.[17] Bempedoic acid is a prodrug that requires activation to bempedoyl CoA by an endogenous enzyme, very long-chain acyl-CoA synthetase-1 (ASCVL1). ASCVL1 is found primarily in the liver and is not detectable in skeletal muscle. Therefore, bempedoic acid is not expected to cause muscle-related adverse effects that are associated with statins.[17] In phase 3 studies, the incidence of skeletal muscle symptoms among patients receiving bempedoic acid were generally comparable to patients receiving placebo.[18-21] Bempedoic acid ACL inhibition has no apparent impact on glucose levels and may be associated with reduced risk of developing diabetes based on results from preclinical, clinical,[18-21] and Mendelian randomization studies.[22] Further data assessing the impact of bempedoic acid on glycemic parameters will come from the fully-enrolled, ongoing CLEAR Outcomes trial (NCT02993406), designed to assess cardiovascular outcomes with bempedoic acid therapy for high cardiovascular risk, statin-intolerant patients,

as approximately 40% of the 14,014 enrolled patients reported type 2 diabetes mellitus at baseline.[23] Bempedoic acid and a bempedoic acid plus ezetimibe fixed-dose combination (BA+EZE FDC; NEXLIZET®, Esperion Therapeutics) are approved and available in the United States as adjuncts to diet and maximally tolerated statin therapy for patients with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH) who require additional LDL-C lowering. In the European Union, bempedoic acid (NILEMDO®, Daiichi Sankyo) and bempedoic acid plus ezetimibe FDC (NUSTENDI®, Daiichi Sankyo) are approved and available with similar labels and additional indications including the ability to use the drug alone in patients who are unable to take a statin.

The objective of this analysis was to describe the efficacy and safety of bempedoic acid in the subgroup of patients with hypercholesterolemia who were previously unable to tolerate any statin dose using pooled data from four phase 3 studies, with a specific focus on muscle-related adverse events (AEs). In addition, this analysis also evaluated similar data from patients who were unable to tolerate any statin from a phase 3 study investigating bempedoic acid plus ezetimibe FDC.

Methods

Study design

This was a post hoc analysis of pooled data from four phase 3, randomized (2 bempedoic acid:1 placebo), double-blind placebo-controlled studies of bempedoic acid including CLEAR Harmony (NCT02666664),[21] CLEAR Wisdom (NCT02991118),[19] CLEAR Serenity (NCT02988115),[20] and CLEAR Tranquility (NCT03001076),[18] which have been previously described in detail. In CLEAR Harmony and CLEAR Wisdom, all patients had ASCVD and/or HeFH and were receiving maximally tolerated statin (which could include no statin), plus or minus other approved lipid-lowering therapy. In CLEAR Serenity, all patients had statin intolerance defined as a patient's inability to tolerate $\geq$ 2 statins (one at the lowest approved starting dose) due to an AE that started or increased during statin therapy and resolved or improved when the statin was discontinued; statin dose was limited to average daily dose less than the lowest approved starting dose. In CLEAR Tranquility, all patients had statin intolerance defined as a patient's inability to tolerate more than the lowest approved starting-dose of a statin. In the bempedoic acid plus ezetimibe FDC study (NCT03337308),[24] patients were taking maximally tolerated statin (which could include no statin) as determined by the investigator. An overview of the design and entry criteria for the four phase 3 bempedoic acid studies and the phase 3 bempedoic acid plus ezetimibe FDC study, which randomized (2:2:2:1) patients to receive either bempedoic acid plus ezetimibe FDC, bempedoic acid, ezetimibe, or placebo, is provided in Fig. 1 and Supplemental Table 1. These studies were conducted in accord with the ethical principles established by the Declaration of Helsinki and Good Clinical Practice guidelines. All protocols were approved by independent ethics committees and all patients provided written informed consent.

Patients

All patients in the four phase 3 bempedoic acid studies who were not receiving any statin therapy were pooled to create the "Phase 3 No Statin Cohort"; these patients could still be receiving other stable lipid-lowering therapy, such as ezetimibe. Patients in the phase 3 bempedoic acid plus ezetimibe FDC study who were not receiving statins were also assessed as the "BA+EZE FDC No Statin Cohort".

Assessments

The prespecified primary efficacy endpoint for all the studies was the percent change from baseline to week 12 in LDL-C. Secondary endpoints included the percent change from baseline to week 12 in total cholesterol, nonhigh-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), and high-sensitivity C-reactive protein (hsCRP). A tertiary endpoint was the percent change from baseline to week 12 in triglycerides. Overall safety was assessed by monitoring treatment-emergent AEs coded using the Medical Dictionary for Regulatory Activities, version 20.1, vital sign measurements, physical examinations, clinical laboratory results, and electrocardiograph readings. The incidences of prespecified muscle-related AEs (muscle necrosis, muscle spasms, muscular weakness, myalgia, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinemia, myoglobinuria, myopathy toxic, myopathy, myositis, necrotizing myositis, pain in extremity, and rhabdomyolysis) were also assessed. Other prespecified AEs of special interest, based on nonclinical or previous clinical findings for bempedoic acid, known effects associated with statins, or other lipid-lowering therapies, or events related to the therapeutic area, included cardiovascular events, decreases in hemoglobin, elevated hepatic enzyme levels, hypoglycemia, metabolic acidosis, neurocognitive disorders, new-onset diabetes/hyperglycemia, renal disorders, and elevations in uric acid and/or the presence of gout (blood uric acid increased, hyperuricemia, and gout).

Statistical analysis

Percent changes from baseline to week 12 in LDL-C, total cholesterol, non-HDL-C, and Apo B levels with bempedoic acid compared with placebo were analyzed using an analysis of covariance with percent change from baseline as the dependent variable, study and treatment as fixed factors, and baseline as a covariate. Differences in percent change in hsCRP from baseline to week 12 with bempedoic acid compared with placebo were analyzed using Wilcoxon rank-sum test with Hodges-Lehmann estimates of location shift and 95% asymptotic confidence limits. Only observed data

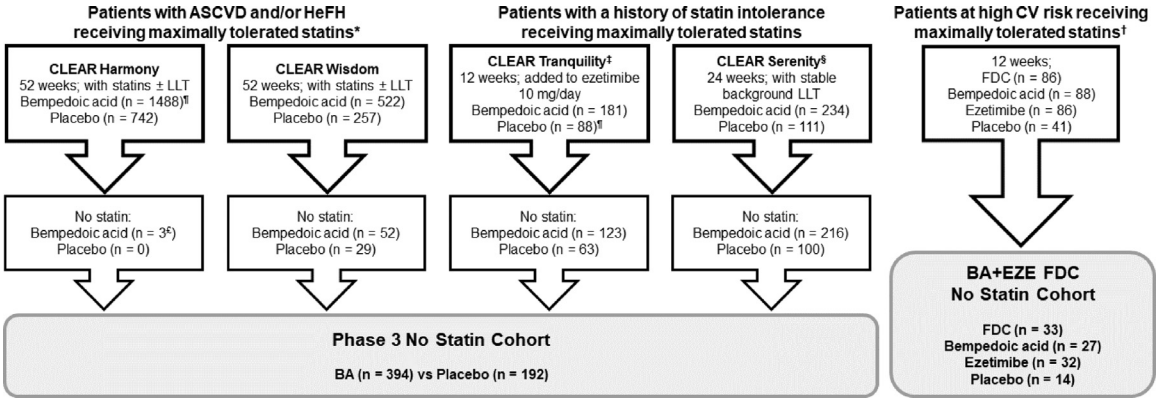

Fig. 1 Patients from phase 3 studies included in the No Statin Cohort.[18-21, 24] AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; FDC, bempedoic acid plus ezetimibe fixed-dose combination; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy. *Maximally tolerated statin dose was determined by the investigator. †Patients enrolled at three study sites were excluded due to data integrity concerns; excluded patients were distributed across the treatment groups. ‡All patients had statin intolerance was defined as a patient's inability to tolerate more than the lowest approved starting-dose of a statin. §All patients had statin intolerance defined as a patient's inability to tolerate ≥ 2 statins (one at the lowest approved starting dose) due to an AE that started or increased during statin therapy and resolved or improved when the statin was discontinued; statin dose was limited to average daily dose less than the lowest approved starting dose. ¶One patient did not receive any dose of study drug and was excluded from the safety population. £These three patients were protocol deviations as all patients were to be receiving background statin therapy.

are included in our analyses. Based on the variation of treatment time across studies, safety data for the Phase 3 No Statin Cohort are reported as exposure-adjusted incidence per 100 person-years (PY). Safety data for the bempedoic acid plus ezetimibe FDC study are reported using descriptive statistics. Statistical analysis was performed using SAS Version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

Results

Phase 3 No Statin Cohort

The Phase 3 No Statin Cohort comprised 586 patients (394 in the bempedoic acid group and 192 in the placebo group). Most patients had been enrolled in CLEAR Serenity (53.9%) and CLEAR Tranquility (31.7%) studies, which reflects the entry criteria of the different studies, with most patients in CLEAR Harmony and CLEAR Wisdom with ASCVD and/or HeFH receiving moderate- and high-intensity statins and CLEAR Serenity and CLEAR Tranquility specifically enrolling patients with a history of statin intolerance. Baseline patient demographics and characteristics for the Phase 3 No Statin Cohort are summarized in Table 1. Overall, the mean (standard deviation [SD]) age was 64.9 (9.9) years and 56.8% of the patients were women. For the overall population, 12.8% of patients had a history of ASCVD, 24.1% had diabetes mellitus, and 67.1% had hypertension. The mean (SD) baseline LDL-C was 148.7 (40.6) mg/dL and the median (Q1, Q3) baseline hsCRP was 2.4 (1.1, 4.5) mg/L; 58.0% of patients were receiving nonstatin background lipid-lowering therapy, primarily ezetimibe. Muscle symptoms were the reason for stopping prior statin therapy for 514 (87.7%) patients.

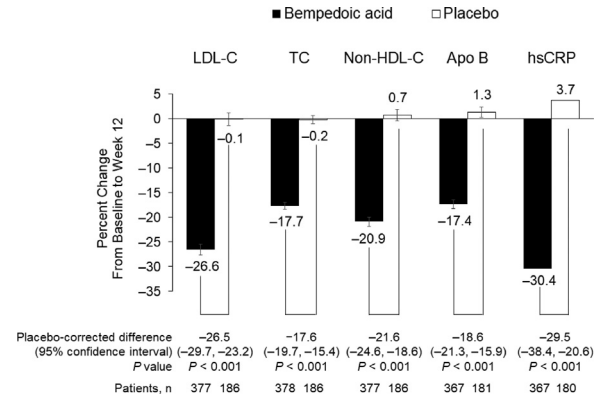

Fig. 2 Change in lipid parameters and hsCRP in the Phase 3 No Statin Cohort. Least squares mean (standard error) percent change from baseline for lipid parameters (LDL-C, TC, non-HDL-C, and Apo B) and median percent change from baseline for hsCRP are shown. Apo B, apolipoprotein B; Non-HDL-C, non–high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

At week 12, bempedoic acid lowered LDL-C levels significantly more than placebo (−26.6% vs −0.1%, respectively; $P < 0.001$) with a placebo-corrected least squares mean difference of −26.5% (95% CI, –29.7% to –23.2%) (Fig. 2), corresponding to an absolute mean (SD) reduction in LDL-C levels by 41.0 (32.6) mg/dL with bempedoic acid and 1.2 (24.7) mg/dL with placebo. The magnitude of LDL-C lowering with bempedoic acid treatment was not altered by the use of lipid-lowering therapy at baseline (interaction, $P = 0.117$).

Absolute LDL-C lowering at week 12 was greater when bempedoic acid was given along with background ezetimibe (mean [SD] absolute reduction of 41.5 [30.3] mg/dL vs 0.4 [23.4] mg/dL for placebo) therapy compared with no background ezetimibe therapy (mean [SD] absolute reduction of

Table 1 Demographics and baseline characteristics, Phase 3 No Statin Cohort.

Characteristic	Bempedoic acid (n = 394)	Placebo (n = 192)
Mean age, years (SD)	64.8 (9.8)	65.0 (10.0)
Male, % (n)	43.1 (170)	43.2 (83)
Race, % (n)		
White	91.9 (362)	85.4 (164)
Black	5.6 (22)	10.4 (20)
Other	2.5 (10)	4.2 (8)
Hispanic or Latino, % (n)	5.8 (23)	5.7 (11)
ASCVD, % (n)	12.7 (50)	13.0 (25)
History of diabetes, % (n)	24.4 (96)	23.4 (45)
History of hypertension, % (n)	66.2 (261)	68.8 (132)
BMI, kg/m^2, mean ± SD	29.9 ± 5.4	30.8 ± 5.6
Total cholesterol, mg/dL, mean ± SD	238.0 ± 46.5	231.8 ± 45.2
Non-HDL-C, mg/dL, mean ± SD	184.6 ± 46.1	177.8 ± 45.0
LDL-C, mg/dL, mean ± SD	150.6 ± 41.3	144.8 ± 39.1
Triglycerides, mg/dL, median (Q1, Q3)	152.0 (111.0, 210.5)	148.3 (112.0, 203.8)
Apo B, mg/dL, mean ± (SD)	136.0 ± 32.1	133.4 ± 30.6
hsCRP, mg/L, median (Q1, Q3)	2.4 (1.1, 4.6)	2.4 (1.1, 4.5)
eGFR category, % (n), mL/min/1.73 m^2		
≥ 90	23.1 (91)	16.1 (31)
≥ 60 to < 90	61.9 (244)	65.1 (125)
≥ 30 to < 60	14.5 (57)	18.8 (36)
< 30	0.5 (2)	0
Reasons for stopping statin prior to enrollment, % (n)*		
Muscle symptoms	86.6 (341)	90.1 (173)
Gastrointestinal symptoms	9.4 (37)	7.3 (14)
Elevated liver enzymes	6.1 (24)	6.8 (13)
Generalized fatigue	4.6 (18)	3.7 (7)
Cognitive decline	3.1 (12)	1.6 (3)
Elevated creatinine kinase	1.3 (5)	2.1 (4)
Depression	0.5 (2)	0.5 (1)
Other	21.1 (83)	21.4 (41)
Background LLT, % (n)	58.1 (229)	57.8 (111)
Ezetimibe	42.9 (169)	43.8 (84)
PCSK9 inhibitor	1.0 (4)	0.5 (1)
Bile acid sequestrant	1.3 (5)	3.1 (6)
Fibrates	4.6 (18)	4.7 (9)
Nicotinic acid and derivatives	2.0 (8)	2.1 (4)
Fish oil†	16.8 (66)	14.1 (27)
Other‡	3.0 (12)	5.2 (10)

Apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; non-HDL-C, non–high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q1, Q3, interquartile range.

*Patients could have more than one reason for stopping prior statin use.

†Includes fish oil, omega-3 fatty acids, omega-3 acid ethyl ester, eicosapentaenoic acid ethyl ester, and eicosapentaenoic acid. Most (94% bempedoic acid, 93% placebo) were nonprescription products.

‡Includes kolestop and sitosterol.

40.5 [34.4] mg/dL vs 1.8 [25.7] mg/dL for placebo; the LS mean placebo-corrected difference in percent change from baseline with bempedoic acid was −30.4% in the presence of ezetimibe and −23.8% in the absence of ezetimibe (interaction $P = 0.0405$) (Fig. 3).

The magnitude of LDL-C lowering with bempedoic acid treatment was not altered by baseline LDL-C levels (< 130 mg/dL vs ≥ 130 mg/dL; (interaction, $P = 0.375$); the difference in percent change of LDL-C from baseline at week 12 between the bempedoic acid group and the placebo group was −28.4% (95% CI, −35.1% to −21.8%) for patients with baseline LDL-C < 130 mg/dL and −25.2% (95% CI, −28.8% to −21.7%) for patients with baseline LDL-C ≥ 130 mg/dL ($P < 0.0001$ for both baseline LDL-C subgroups). At week 12, the percent change from baseline in total cholesterol, non-HDL-C, Apo B, and hsCRP were also all significantly greater with bempedoic acid compared with placebo ($P < 0.001$ for all). The median (Q1, Q3) percent change

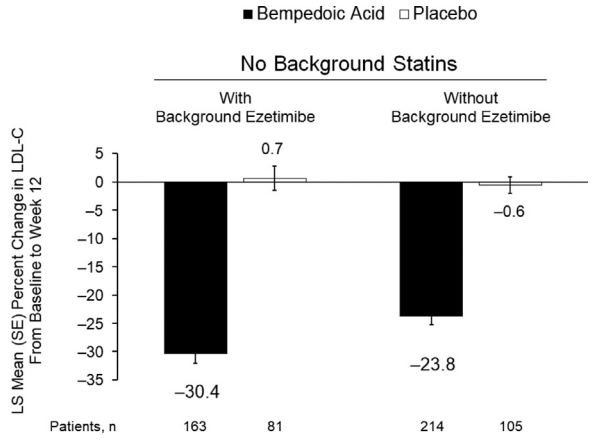

Fig. 3 Change in LDL-C in the presence or absence of background ezetimibe in the Phase 3 No Statin Cohort. Least squares mean (standard error [SE]) percent change from baseline. LDL-C, low-density lipoprotein cholesterol.

from baseline at week 12 for triglycerides was 0.40 (-18.18, 25.61) for the bempedoic acid group and 1.31 (-12.69, 18.41) for the placebo group.

BA+EZE FDC No Statin Cohort

Overall, 106 (35.2%) of the 301 patients in the bempedoic acid plus ezetimibe FDC study were not taking statins at baseline, including 33 who were randomized to receive bempedoic acid plus ezetimibe FDC, 27 to bempedoic acid alone, 32 to ezetimibe alone, and 14 to placebo. Baseline demographics and characteristics for the BA+EZE FDC No Statin Cohort are summarized in Supplemental Table 2. The mean baseline LDL-C in this cohort was 168.6 mg/dL.

At week 12, bempedoic acid plus ezetimibe FDC lowered LDL-C levels in the FDC No Statin Cohort significantly more than placebo (−38.8% vs 0.4%), for a placebo-corrected least squares mean difference of –39.2% (95% CI, –51.7% to –26.7%; $P < 0.001$) (Fig. 4A). The mean (SD) absolute reduction in LDL-C with bempedoic acid plus ezetimibe FDC was 68.3 (44.1) mg/dL compared with 0.0 (25.6) mg/dL with placebo. Improvements in total cholesterol, non-HDL-C, Apo B, and hsCRP with bempedoic acid plus ezetimibe FDC compared with placebo were also observed at week 12 (Fig. 4B-4E). The reduction from baseline in LDL-C, total cholesterol, and non-HDL cholesterol with bempedoic acid plus ezetimibe FDC were significantly greater than with bempedoic acid alone or ezetimibe alone (all $P < 0.01$). The reductions in Apo B and hsCRP with bempedoic acid plus ezetimibe FDC were also significantly greater than with ezetimibe alone ($P = 0.025$ and $P = 0.010$, respectively); there was no statistically significant difference between bempedoic acid plus ezetimibe FDC and bempedoic acid alone for Apo B or hsCRP lowering.

Safety

In the Phase 3 No Statin Cohort, treatment-emergent AEs occurred at an incidence rate of 137.0 per 100 PY in patients receiving bempedoic acid and 117.0 per 100 PY in those receiving placebo (Table 2). The incidence for serious AEs among patients treated with bempedoic acid was comparable to that among patients receiving placebo. Treatment-emergent AEs leading to discontinuation of study drug occurred at a rate of 32.8 per 100 PY and 24.3 per 100 PY with bempedoic acid and placebo, respectively. The most common reason for discontinuation of study drug was myalgia with an incidence of 5.8 per 100 PY for patients treated with bempedoic acid and 10.6 per 100 PY for patients receiving placebo.

AEs of special interest among patients in the Phase 3 No Statin Cohort are summarized in Table 3. Muscle-related disorders occurred at an incidence rate of 26.4 and 28.6 per 100 PY with bempedoic acid and placebo, respectively. Among the patients (bempedoic acid, n = 341; placebo, n = 173) who were not taking a statin due to prior muscle symptoms, 46 (13.5%) treated with bempedoic acid and 26 (15.0%) receiving placebo reported a muscle-related disorder during the bempedoic acid phase 3 studies. Myalgia was reported at lower rates among patients treated with bempedoic acid compared with patients receiving placebo (9.5 vs 14.8 per 100 PY). In contrast, pain in the extremity was reported more frequently with bempedoic acid (6.9 per 100 PY) than with placebo (4.2 per 100 PY). Muscular weakness was reported by two patients treated with bempedoic acid (1.1 per 100 PY) and two patients receiving placebo (2.1 per 100 PY). One patient in each treatment group had a creatinine kinase level > 5 × the upper limit of normal (ULN) (Supplementary Table 3).

Other laboratory abnormalities and values for the Phase 3 No Statin Cohort are also summarized in Supplemental Tables 3 and 4. Increases in alanine aminotransferase and/or aspartate aminotransaminase levels > 5 × ULN occurred in two (0.5%) patients treated with bempedoic acid and in no patients treated with placebo. No patients in either treatment arm had elevations in liver enzyme levels that met the criteria for Hy's law (aminotransferase levels > 3 × ULN and concomitant total bilirubin > 2 × ULN), or elevations in total bilirubin > 2 times ULN. Four (1.0%) patients randomized to bempedoic acid, and no patients randomized to placebo discontinued study drug due to increased liver function tests. After 4 weeks of treatment with bempedoic acid, mean (SD) uric acid levels increased by 14.0% (14.4) with bempedoic acid compared with a mean (SD) increase of 1.4% (13.1) for patients receiving placebo. The increase in uric acid with bempedoic acid treatment observed at week 4 was stable through week 12. The incidence of gout was 3.2 per 100 PY in the bempedoic acid group and 1.1 per 100 PY in the placebo group. Decreases in hemoglobin ≥ 2 g/dL and less than the lower limit of normal were observed in six (1.5%) patients randomized to bempedoic acid and one (0.5%) patient randomized to placebo; the incidence of anemia was 1.6 per 100 PY in the bempedoic acid group and there were no cases of anemia in the placebo group. The rates of new onset or worsening of diabetes, renal disorders, hypoglycemia, and neurocognitive disorders were comparable

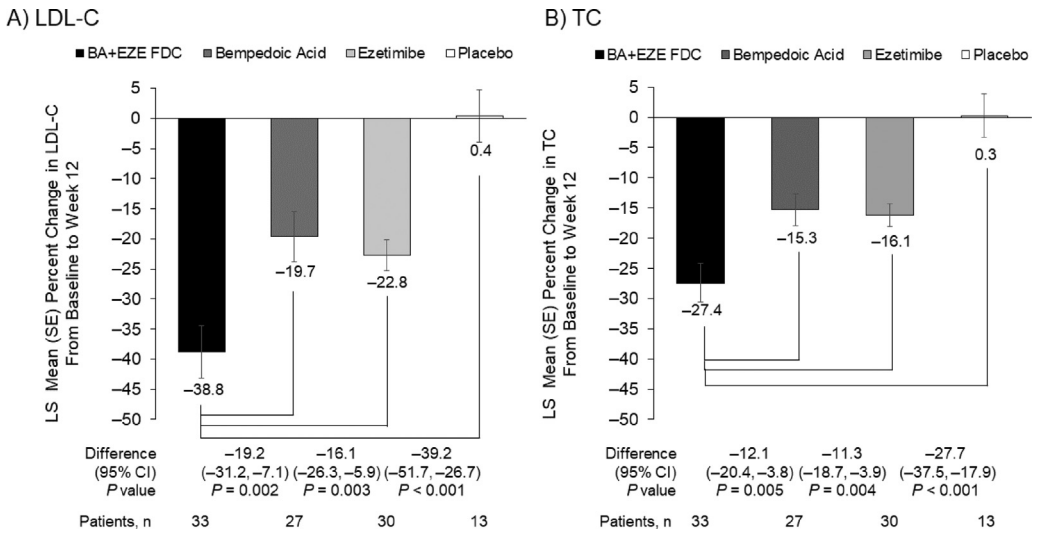

Fig. 4 Change in lipid parameters and hsCRP in the BA + EZE FDC No Statin Cohort. Least squares mean (standard error [SE]) percent change from baseline for lipid parameters and median percent change from baseline for hsCRP are shown. Apo B, apolipoprotein B; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; TC, total cholesterol.

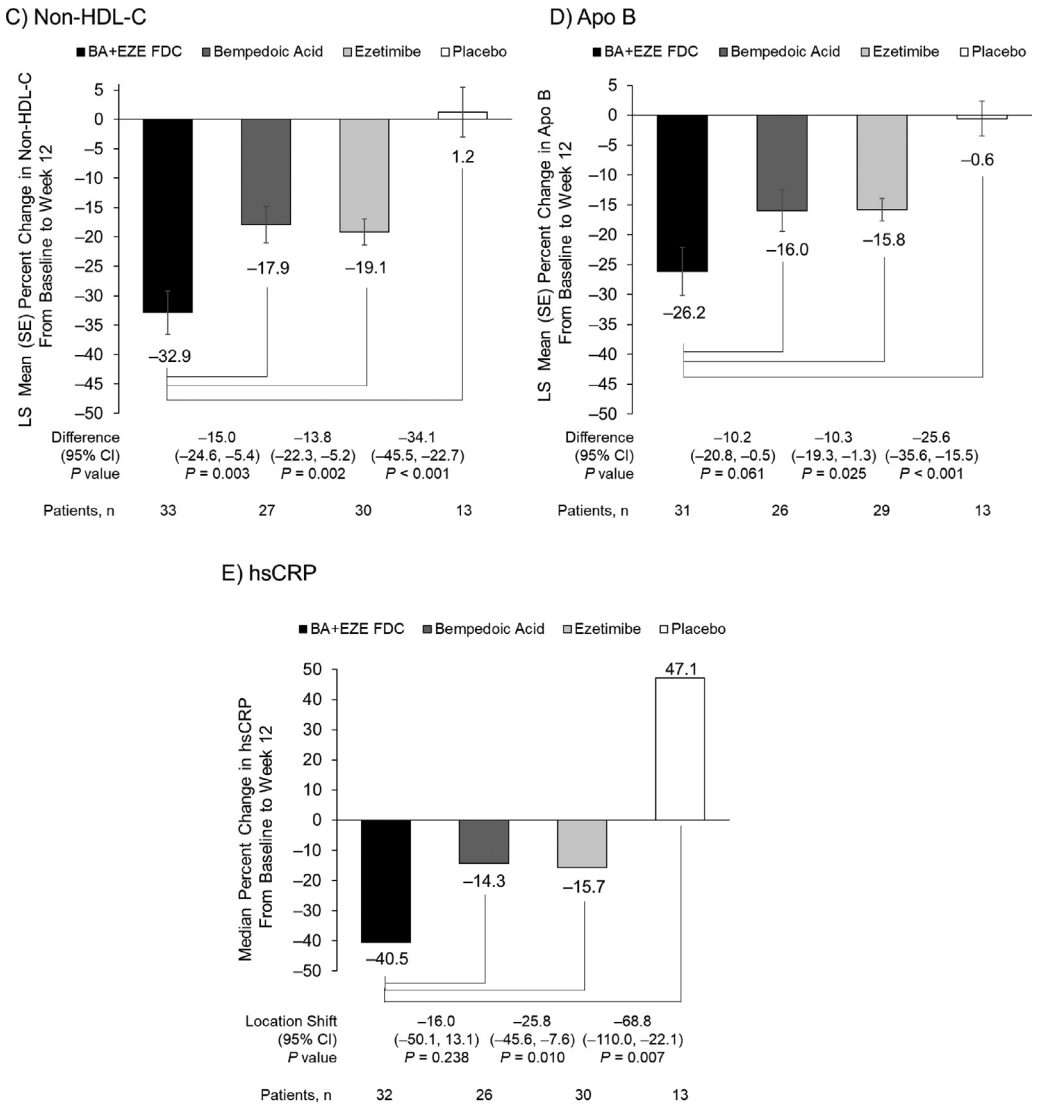

Fig. 4 Continued

Table 2 Treatment-emergent adverse events, Phase 3 No Statin Cohort.

Parameter	Exposure-adjusted incidence per 100 person-years (n)	
	Bempedoic acid (n = 394)	Placebo (n = 192)
Any TEAE	137.0 (259)	117.0 (111)
Serious TEAE	14.8 (28)	13.8 (13)
TEAE related to study drug	51.3 (97)	38.1 (36)
TEAE by maximum severity		
Mild	61.4 (116)	51.8 (49)
Moderate	60.8 (115)	50.8 (48)
Severe	14.8 (28)	14.8 (14)
TEAE leading to IMP discontinuation	32.8 (62)	24.3 (23)
Most common TEAEs leading to discontinuation (occurring in > 2% of patients)		
Myalgia	5.8 (11)	10.6 (10)
Muscle spasms	3.2 (6)	0
Arthralgia	2.6 (5)	1.1 (1)
Fatigue	2.1 (4)	2.1 (2)
Headache	2.1 (4)	0
TEAE with a fatal outcome	0	1.1 (1)

IMP, investigational medicinal product; TEAE, treatment-emergent adverse event.

Table 3 Adverse events of special interest, Phase 3 No Statin Cohort.

Parameter	Exposure-adjusted incidence per 100 person-years, (n)	
	Bempedoic acid (n = 394)	Placebo (n = 192)
Muscular disorders	26.4 (50)	28.6 (27)
Myalgia	9.5 (18)	14.8 (14)
Muscle spasms	8.5 (16)	7.4 (7)
Pain in extremity	6.9 (13)	4.2 (4)
Blood creatine kinase increased	4.2 (8)	1.1 (1)
Muscular weakness	1.1 (2)	2.1 (2)
Uric acid elevations/gout	14.8 (28)	4.2 (4)
Blood uric acid increased	11.1 (21)	3.2 (3)
Gout	3.2 (6)	1.1 (1)
Hyperuricemia	1.1 (2)	0
Hepatic enzyme elevation	8.5 (16)	2.1 (2)
New-onset diabetes/hyperglycemia	4.8 (9)	5.3 (5)
Renal disorders	4.2 (8)	3.2 (3)
Hemoglobin decreased	2.1 (4)	0
Hypoglycemia	1.1 (2)	2.1 (2)
Neurocognitive disorders	1.1 (2)	1.1 (1)

in both treatment groups, and there were no cases of tendon rupture.

The incidence of AEs (Table 4) and laboratory abnormalities (Supplemental Tables 3 and 4) in the BA+EZE FDC No Statin Cohort followed a comparable pattern to that reported for the Phase 3 No Statin Cohort.

Discussion

In this post hoc analysis of patients who were unable to tolerate any dose of statin, bempedoic acid lowered LDL-C levels by an average of 26.5% compared with placebo. In comparison, bempedoic acid lowered LDL-C levels by a mean of 17.8% among patients who were receiving maximally tolerated background statin in the parent studies, 91% of whom were receiving moderate to high doses of a statin.[25] The greater reduction in LDL-C in the absence of background statin may be due to the shared pathway of inhibition between bempedoic acid and statins with bempedoic acid inhibiting cholesterol synthesis upstream of statins. Other less likely potential contributors to the difference in LDL-C lowering between those two populations include a difference in the use of other background lipid-lowering therapies (approximately 15% of the patients in the maximally tolerated statin group were receiving other non-statin background

Table 4 Treatment-emergent adverse events, Bempedoic Acid Plus Ezetimibe FDC No Statin Cohort.

Parameter	Patients, % (n)			
	Bempedoic acid + ezetimibe FDC (n = 33)	Bempedoic acid (n = 27)	Ezetimibe (n = 32)	Placebo (n = 14)
Any AE	75.8 (25)	77.8 (21)	68.8 (22)	42.9 (6)
Serious AE	3.0 (1)	11.1 (3)	9.4 (3)	7.1 (1)
AE related to study drug	18.2 (6)	22.2 (6)	3.1 (1)	21.4 (3)
AE by maximum severity				
Mild	36.4 (12)	44.4 (12)	37.5 (12)	21.4 (3)
Moderate	36.4 (12)	25.9 (7)	25.0 (8)	14.3 (2)
Severe	3.0 (1)	7.4 (2)	6.3 (2)	7.1 (1)
Drug discontinuation due to an AE	9.1 (3)	11.1 (3)	12.5 (4)	0
Most common AEs leading to discontinuation occurring in > 1 patient in any group				
Myalgia	0	11.1 (3)	0	0
AE with a fatal outcome	0	0	0	0
TEAEs of special interest				
Muscular disorders	6.1 (2)	11.1 (3)	12.5 (4)	7.1 (1)
Myalgia	0	11.1 (3)	3.1 (1)	7.1 (1)
Muscle spasms	3.0 (1)	0	6.3 (2)	0
Pain in extremity	3.0 (1)	0	3.1 (1)	0
Renal disorders	3.0 (1)	0	0	0
Neurocognitive disorders	0	3.7 (1)	0	0
Hypoglycemia	0	3.7 (1)	0	0

AE, adverse event; FDC, fixed-dose combination; TEAE, treatment-emergent adverse event.

lipid-lowering therapies compared with approximately 60% of the patients in the low-dose or no statin group) or differences in baseline demographics (the maximally tolerated statin group had approximately 30% fewer women).

More than half (58%) of the patients in the Phase 3 No Statin Cohort were receiving concurrent lipid-lowering therapy, most commonly ezetimibe. In a previous phase 3 pooled analysis based on eligibility criteria including maximally tolerated statin and cardiovascular risk and a higher number of patients, background ezetimibe use with bempedoic acid was not associated with greater LDL-C lowering among patients with ASCVD and/or HeFH receiving maximally tolerated statin (interaction $P = 0.15$) or patients with a history of statin intolerance who were taking low-dose, very low-dose, or no statin (interaction $P = 0.12$).[25] In the current subgroup analysis, which is based on a smaller number of patients taking no statin at all, concomitant use of ezetimibe augmented lowering of LDL-C with bempedoic acid (interaction $P = 0.0405$). Greater LDL-C lowering with bempedoic acid in the absence of a statin but presence of ezetimibe may be due to complementary mechanisms between inhibition of cholesterol synthesis by bempedoic acid and inhibition of cholesterol absorption by ezetimibe, both leading to upregulation of LDL receptors[26] or a difference in adherence to taking a study drug versus background medication. When bempedoic acid was administered as a fixed-combination with ezetimibe among patients unable to take statins, LDL-C levels were reduced relative to placebo by 39.2%, significantly greater than with bempedoic acid or ezetimibe alone ($P < 0.0001$). Similar to statin and ezetimibe FDCs, which are more effective at lowering LDL-C than when a statin and ezetimibe are administered as separate pills,[27] a greater reduction in LDL-C with bempedoic acid plus ezetimibe FDC compared with bempedoic acid or ezetimibe alone may be due to the complementary mechanisms of the two drugs and improved drug adherence. For patients unable to take a statin who continue to have suboptimal lowering of LDL-C levels, bempedoic acid alone or in combination with ezetimibe may be an attractive treatment regimen.

Bempedoic acid also lowered total cholesterol, non-HDL-C, Apo B, and hsCRP, as observed in each of the four phase 3 bempedoic acid studies.[19-21,24] The reduction in hsCRP with bempedoic acid treatment in the absence of a statin or presence of low-dose statin was comparable to reductions in hsCRP reported for a statin alone or a statin in combination with ezetimibe (10%–40%).[28-31]

Patients who are unable or unwilling to take a statin despite careful work-up represent a challenging-to-treat patient population. Results from our analysis showed that despite the history of statin-related muscle adverse reactions in the study cohort, muscle-related AEs with bempedoic acid were reported at a lower rate compared with placebo (26.4 per 100 PY vs 28.6 per 100 PY). The most common reasons for discontinuation of bempedoic acid treatment were myalgia, muscle spasms, and arthralgia. The rate of discontinuation due to myalgia was lower among patients treated with bempedoic acid compared with those receiving placebo. These findings are consistent with the safety and tolerability profile of bempedoic acid across the entire phase 3 program.[32] In this Phase 3 No Statin Cohort, pain

in the extremity was reported more frequently with bempedoic acid (6.9 per 100 PY) than with placebo (4.2 per 100 PY). There was no increase in muscle-related AEs with the combination of bempedoic acid plus ezetimibe. A potential explanation for the lack of excess muscle-related symptoms with bempedoic acid compared with placebo in this cohort of patients unable to take a statin may relate to the differences in pharmacology of bempedoic acid and statins. Bempedoic acid is a pro-drug that is converted to its active form by the enzyme ASCVL1, which is expressed primarily in liver and kidney, but not in skeletal muscle or other tissues.[17,33] As a result, the activity of bempedoic acid on cholesterol synthesis is likely to be primarily localized in the liver.

Stains may also be associated with hepatic adverse reactions including temporary elevations in transaminases, which occur in up to 3% of statin-treated patients; however, drug-induced liver injury is extremely rare and without confirmed causality.[34,35] Among patients in the Phase 3 No Statin Cohort, alanine aminotransferase and/or aspartate transaminase levels $> 5 \times$ ULN occurred in 0.5% of patients treated with bempedoic acid and no patients receiving placebo. This finding was consistent with previous findings with bempedoic acid[32] and comparable to the effects of statins[36] or ezetimibe on transaminase levels.[37] The incidence of other AEs sometimes associated with statin treatment including incident diabetes mellitus, or neurocognitive disorders, was no greater with bempedoic acid than with placebo in this cohort of patients unable to take a statin. Among patients in the Phase 3 No Statin Cohort, the incidence of gout was 3.2 per 100 PY in the bempedoic acid group and 1.1 per 100 PY in the placebo group.[32] Bempedoic acid is associated with small but reversible increases in uric acid levels, likely due to inhibition of organic anion transporter 2.[32]

There are limitations of this analysis. This post hoc analysis evaluated the subset of patients not taking concomitant statins enrolled in four phase 3 clinical trials of bempedoic acid. The lack of statin in this subset may have accounted for the increased elevated baseline LDL-C levels. Also, the populations included in the parent studies from which this subset was derived were different, with two studies focusing on patients with a history of ASCVD and/or HeFH receiving moderate- or high-intensity statins (which may have included no statin)[19,21] and two studies focusing on patients with a history of statin intolerance with varying degrees of cardiovascular risk (primary prevention or ASCVD and/or HeFH).[18,20] Most of the patients in this analysis were White, which may limit generalizability of the results. Most of the patients in the current analysis came from the two relatively small studies focusing on statin intolerance. As a result, the total population included in our analysis was too small for meaningful subgroup analyses. Importantly, all four studies in the Phase 3 No Statin Cohort followed the same randomization design, had the same primary efficacy endpoint and assessed safety with the same endpoints. Because of the relatively small number of patients evaluated, aspects of safety are difficult to assess compared with placebo given that some AEs and AEs of special interest were reported for only a few patients. But the safety findings were similar to the safety findings in the overall development program and no unexpected AEs were noted.

Despite the high incidence of statin-associated symptoms, evidence from randomized studies of oral treatment options in this challenging-to-treat patient population is sparse. This investigation of patients unable to take a statin is of particular importance as many previous studies have specifically excluded patients with a history of statin tolerance problems.[38,39] Bempedoic acid either alone or in combination with ezetimibe provides an additional option for LDL-C−lowering among the large and difficult-to-treat population of patients with hypercholesterolemia and elevated cardiovascular risk who also have statin tolerance problems. Data from the ongoing CLEAR Outcomes, a long-term study of cardiovascular outcomes in patients with or at high risk for ASCVD and who reported adverse reactions that started or increased during statin therapy and resolved or improved when statin therapy was discontinued, will provide further insights into the role of bempedoic acid in this population.[23]

In conclusion, both bempedoic acid and bempedoic acid plus ezetimibe FDC provide effective and well-tolerated treatment options for statin-intolerant patients.

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A.M.G. is an Esperion board member and Akcea Data and Safety Monitoring Board chair and has also served as a consultant for Kowa.

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L.T.B. and Y.Z. are employees of Esperion Therapeutics, Inc., and may own Esperion stock and/or stock options.

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All authors participated in data interpretation, approved the final manuscript draft submitted for publication and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the publication.

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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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.03.001.

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