FACTORS INFLUENCING BEMPEDOIC ACID–MEDIATED REDUCTIONS IN HIGH SENSITIVITY C-REACTIVE PROTEIN: ANALYSIS OF POOLED PATIENT-LEVEL DATA FROM 4 PHASE 3 CLINICAL TRIALS

Erik S. G. Stroes[1], Harold E. Bays[2], Maciej Banach[3], Alberico L. Catapano[4], P. Barton Duell[5], Ulrich Laufs[6], G. B. John Mancini[7], Kausik K. Ray[8], William J. Sasiela[9], Zhan Ye[9], Antonio M. Gotto, Jr[10]

[1]Department of Vascular Medicine, Academic Medical Centre, Amsterdam, the Netherlands; [2]Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY, USA; [3]Department of Hypertension, Medical University of Łódź and Polish Mother's Memorial Hospital Research Institute (PMMHRI), Łódź, Poland; [4]University of Milan and Multimedica IRCCS, Milan, Italy; [5]Knight Cardiovascular Institute, School of Medicine, Oregon Health and Science University, Portland, OR, USA; [6]Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Leipzig, Germany; [7]Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada; [8]Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, London, UK; [9]Esperion Therapeutics, Inc., Ann Arbor, MI, USA; [10]Houston Methodist Research Institute, Houston, Texas, USA; and Weill Cornell Medicine, New York, NY, USA

BACKGROUND

- Lower high-sensitivity C-reactive protein (hsCRP) levels are associated with a reduced risk for atherosclerotic cardiovascular disease (ASCVD)[1–3]
- Statin-induced hsCRP reduction is associated with ASCVD risk reduction, independent of changes in low-density lipoprotein cholesterol (LDL-C)[4]
- Bempedoic acid is an oral ATP-citrate lyase inhibitor that significantly lowers LDL-C levels in patients with hypercholesterolemia
- Results from 4 randomized placebo-controlled phase 3 studies demonstrated consistent reductions in hsCRP with bempedoic acid[5–8]

OBJECTIVE

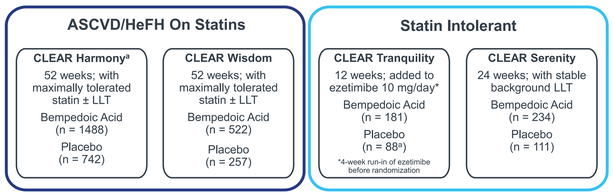
- To assess the role of baseline hsCRP and background statin intensity on bempedoic acid–mediated reductions in hsCRP in patients with hypercholesterolemia

METHODS

Study Design and Treatment

- Data were pooled from 4 phase 3 clinical trials in which patients with hypercholesterolemia were randomized 2:1 to treatment with bempedoic acid 180 mg or placebo **(Figure 1)**
  - Two studies enrolled patients with ASCVD and/or heterozygous familial hypercholesterolemia (HeFH) who were receiving maximally tolerated statin therapy (ASCVD/HeFH on statins pool)[4,5]
  - Two studies enrolled patients with a history of statin intolerance (statin intolerant pool), defined as inability to tolerate 1 or more statin (CLEAR Tranquility), or inability to tolerate 2 or more statins, 1 at a low dose, due to an adverse event (CLEAR Serenity)[6,7]

Figure 1. Studies Included in the Pooled Efficacy Analysis



[a]One patient did not receive any dose of study drug and was excluded from the analysis population. In CLEAR Tranquility, patients who experienced a study drug–related adverse event during the placebo and ezetimibe run-in period did not proceed to randomization.
ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LLT = lipid-lowering therapy.

Assessments

- Mean percent change from baseline to week 12 in LDL-C levels was the primary efficacy endpoint for the studies
- Median percent change from baseline to week 12 in hsCRP levels was a secondary endpoint of the 4 Phase 3 trials
- The integrated analysis of all 4 studies examined the effect of bempedoic acid on hsCRP at week 12 in patients stratified by baseline hsCRP < 2 mg/L or ≥ 2 mg/L, respectively

RESULTS

Patients

- hsCRP levels were reported for 3606 patients at baseline and week 12
- Baseline characteristics were generally similar across baseline hsCRP subgroups, with a few notable differences **(Table 1)**:
  - hsCRP ≥ 2 mg/dL had a greater percentage of patients with:
    - Higher baseline hsCRP
    - Higher baseline body mass index
    - Hypertension
    - History of diabetes
    - No statins
  - hsCRP ≥ 2 mg/dL had a smaller percentage of patients with:
    - History of ASCVD
    - High-statin intensity
- Among patients in the ASCVD/HeFH on statins pool (n = 3003), 1237 (41.2%) had baseline hsCRP levels ≥ 2 mg/L and 1766 (58.8%) had baseline hsCRP levels < 2 mg/L
- Among statin intolerant patients (n = 603), 355 (58.9%) had baseline hsCRP levels ≥ 2 mg/L and 248 (41.1%) had baseline hsCRP levels < 2 mg/L

Table 1. Baseline Demographics and Characteristics Stratified by Baseline hsCRP

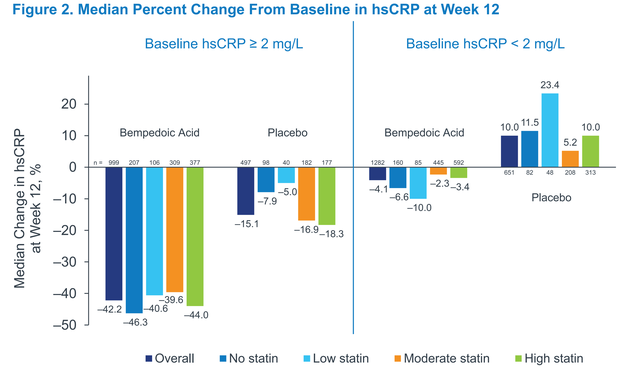
	hsCRP < 2 mg/L		hsCRP ≥ 2 mg/L	
Characteristic	Bempedoic Acid (n = 1348)	Placebo (n = 666)	Bempedoic Acid (n = 1070)	Placebo (n =522)
Age, years, mean (SD)	65.6 (9.5)	66.5 (8.8)	64.7 (9.0)	65.2 (9.1)
Male, % (n)	71.4 (963)	71.2 (474)	59.3 (634)	58.0 (303)
Race, % (n)				
White	96.3 (1298)	94.6 (630)	92.1 (985)	94.4 (493)
Black	2.2 (29)	3.5 (23)	6.0 (64)	4.2 (22)
Asian	0.9 (12)	1.1 (7)	1.4 (15)	0.8 (4)
Other	0.7 (9)	0.9 (6)	0.6 (6)	0.6 (3)
Hispanic or Latino, % (n)	3.8 (51)	2.9 (19)	6.7 (72)	7.1 (37)
Body mass index, kg/m^2, mean (SD)	28.7 (4.3)[a]	28.7 (4.3)	31.3 (5.5)[b]	31.3 (5.5)[c]
History of hypertension, % (n)	74.6 (1006)	77.5 (516)	81.3 (870)	80.8 (422)
History of diabetes, % (n)	24.0 (323)	24.2 (161)	33.2 (355)	33.0 (172)
CVD risk, % (n)				
ASCVD only	84.9 (1144)	85.6 (570)	75.2 (805)	76.8 (401)
HeFH (with or without ASCVD)	3.7 (50)	3.3 (22)	2.4 (26)	2.7 (14)
LDL-C, mg/dL, mean (SD)	110.0 (34.8)	108.8 (34.1)	119.5 (38.1)	118.2 (38.7)
hsCRP, mg/L, mean (SD)	0.96 (0.49)	0.98 (0.50)	6.9 (11.9)	6.6 (8.8)
Baseline statin intensity, % (n)				
No	14.3 (193)	14.6 (97)	25.5 (273)	23.8 (124)
Low	4.7 (64)	5.4 (36)	5.6 (60)	4.4 (23)
Moderate	34.9 (471)	32.1 (214)	31.7 (339)	36.2 (189)
High	46.0 (620)	47.9 (319)	37.2 (398)	35.6 (186)

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; hsCRP = high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SD = standard deviation.
[a]n = 1347. [b]n = 1069. [c]n = 521.

Reductions in hsCRP With Bempedoic Acid

- In individual studies, median hsCRP was significantly reduced from baseline to week 12 by a range of 18.7% to 32.5% in patients treated with bempedoic acid
- In the pooled analysis, median hsCRP reduction with bempedoic acid was greater in patients with baseline values ≥ 2 mg/L (–42.2%) than in patients with baseline hsCRP < 2 mg/L (–4.1%) values. This response was not influenced by background statin intensity **(Figure 2)**

Figure 2. Median Percent Change From Baseline in hsCRP at Week 12

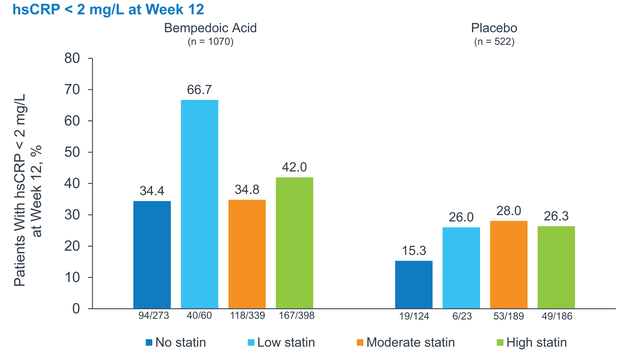


hsCRP = high-sensitivity C-reactive protein.

Achieving hsCRP < 2 mg/L With Bempedoic Acid

- Among patients with baseline hsCRP ≥ 2 mg/L, 419 (39.2%) of the 1070 patients treated with bempedoic acid and 127 (24.3%) of the 522 patients receiving placebo achieved hsCRP levels < 2 mg/L at week 12
- A larger percentage of patients who received bempedoic acid achieved hsCRP levels < 2 mg/L at week 12 compared with patients who received placebo **(Figure 3)**

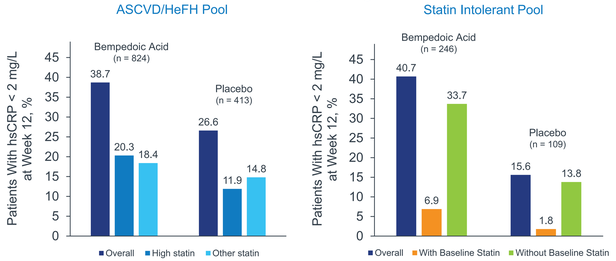
Figure 3. Proportion of Patients With Baseline hsCRP Levels ≥ 2 mg/L Who Achieved hsCRP < 2 mg/L at Week 12



BA = bempedoic acid; hsCRP = high-sensitivity C-reactive protein.

- Among patients with baseline hsCRP ≥ 2 mg/L treated with bempedoic acid, 319 (38.7%) patients in the ASCVD/HeFH pool (n = 824) and 100 (40.7%) patients in the statin intolerant pool (n = 246) had hsCRP < 2 mg/L at week 12 **(Figure 4)**
- 33.7% of patients receiving bempedoic acid in the statin intolerant pool (who were receiving no statins, low-dose, or very-low-dose statins) achieved hsCRP < 2 mg/L at week 12 compared with 13.8% of patients receiving placebo in the statin intolerant pool

Figure 4. Proportion of Patients With Baseline hsCRP Levels ≥ 2 mg/L at Baseline Who Achieved hsCRP < 2 mg/L at Week 12 by Background Statin Therapy



ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia.

Safety

- The safety profile was similar across subgroups based on baseline hsCRP **(Table 3)**

Table 3. Treatment-Emergent Adverse Events, Safety Population

	Patients, % (n)			
	hsCRP < 2 mg/L		hsCRP ≥ 2 mg/L	
Parameter	Bempedoic Acid (n = 1347)	Placebo (n = 666)	Bempedoic Acid (n = 1070)	Placebo (n = 522)
Any TEAE[a]	74.1 (998)	73.7 (491)	71.7 (767)	71.1 (371)
Serious AE	13.7 (184)	13.2 (88)	14.7 (157)	13.4 (70)
Treatment-related AE	24.5 (330)	20.9 (139)	23.2 (248)	19.7 (103)
TEAE leading to discontinuation of study drug	10.8 (145)	6.6 (44)	11.7 (125)	9.2 (48)
TEAE resulting in death	0.7 (10)	0.2 (1)	0.8 (9)	0.6 (3)

AE = adverse event; TEAE = treatment-emergent adverse event.
[a]AEs were coded according to Medical Dictionary of Regulatory Activities (MedDRA) version 20.1.

CONCLUSIONS

- Bempedoic acid significantly lowers hsCRP in patients with hypercholesterolemia, regardless of the presence or intensity of background statin therapy
- When compared with patients who had baseline hsCRP < 2 mg/L
  - More patients with baseline hsCRP ≥ 2 mg/L had a history of diabetes and were not taking statins at baseline
  - Fewer patients had a history of ASCVD/or were taking high-intensity statin
- Greatest predictor of the magnitude of hsCRP reduction was baseline hsCRP level
- Among patients with baseline hsCRP ≥ 2 mg/L, a greater proportion of patients treated with bempedoic acid achieved hsCRP < 2 mg/L at week 12 compared with placebo
- The effect of bempedoic acid–mediated hsCRP reduction on CVD risk reduction is currently being assessed in an ongoing cardiovascular outcomes trial (NCT02993406)

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DISCLOSURES

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