Long-term Safety, Tolerability, and Efficacy of Bempedoic Acid vs Placebo in High Cardiovascular Risk Patients with LDL-C Above 1.8 mmol/L on Maximally Tolerated Statin Therapy (CLEAR Harmony)

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on behalf of the CLEAR Harmony Steering Committee:

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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (AbbVie, Akcea, Algorithm, Amgen, AstraZeneca, Boehringer Ingelheim, Cerenis, Cipla, Kowa, Medco, MSD, Novo Nordisk, Pfizer, Regeneron, Resverlogix, Sanofi, and Takeda)

Disclosures

The CLEAR Harmony clinical trial was funded by Esperion Therapeutics, Inc.

Individual disclosures*

- KK Ray: AbbVie, Akcea, Algorithm, Amgen, AstraZeneca, Boehringer Ingelheim, Cerenis, Cipla, Kowa, Medco, MSD, Novo Nordisk, Pfizer, Regeneron, Resverlogix, Sanofi, and Takeda
- HE Bays: Aegerion, Amgen, LIB Therapeutics, Merck, Regeneron, and Sanofi
- AL Catapano: AstraZeneca, Amgen, Genzyme, Mediolanum, Sanofi, Merck, Rottapharm, Recordati, Sigma-Tau, Pfizer, Regeneron, Menarini, Kowa, and Eli Lilly
- N Lalwani, LT Bloedon, and LR Sterling are employees of Esperion
- CM Ballantyne: Abbott Diagnostic, Akcea, Amarin, Amgen, Esperion, Gilead, Matinas BioPharma, Inc., Merck, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, NIH, AHA, and ADA

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Background

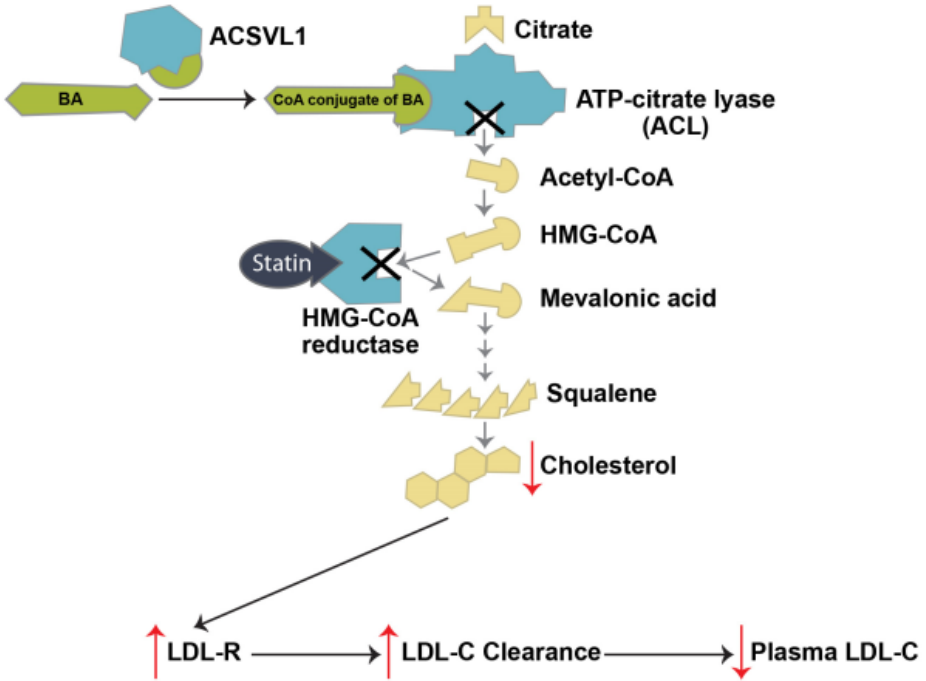
- Lipid-lowering therapies (primarily statins) have significantly reduced CVD burden[1]
- However, statins alone may be insufficient to achieve optimal LDL-C levels[2-5]
  - Inadequate treatment response
  - Intolerance to statins or a higher-intensity statin regimen
- Many patients require additional therapies such as bile acid sequestrants, ezetimibe, or PCSK9 monoclonal antibodies
- Patients may not achieve goals despite combination lipid-lowering therapy, and the uptake of monoclonal antibodies has been limited due to cost
- Additional safe and effective options are needed to address unmet needs and complement existing lipid-lowering therapies

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

1. Ford ES, et al. *N Engl J Med.* 2007;356:2388-98; 2. Stone NJ, et al. *Circulation.* 2014;129:S1-45; 3. Jacobson TA, et al. *J Clin Lipidol.* 2015;9:129-69; 4. Danese MD, et al. *BMJ Open.* 2017;7:e013851; 5. Steen DL, et al. *BMJ Open.* 2017;7:e013255.

Bempedoic Acid Mechanism of Action

Converted to the CoA Conjugate of Bempedoic Acid, the Active Form, Only in Liver



- Bempedoic acid (BA) acts in the same cholesterol biosynthesis pathway as statins
- BA targets ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Upregulates LDL receptors and lowers LDL-C
- Specific isozyme (ACSVL1) that converts BA into an active drug is not present in skeletal muscle

ACSVL1, very long-chain acyl-CoA synthetase-1; CoA, coenzyme A; LDL, low-density lipoprotein.

Prior Experience With BA

- 10 studies conducted with approximately 1,200 patients
  - Most patients treated for 12 weeks
  - Well tolerated but limited exposure
    - In the largest prior study, 250 patients received BA ± ezetimibe for 12 weeks[1]
- Efficacy (180 mg dose)
  - LDL-C reduction of ~30% as a monotherapy[2]
  - LDL-C reduction of ~50% when combined with ezetimibe[1]
  - Incremental LDL-C reduction of 20+% when added to stable statin therapy[3]
- Guidelines advocate moderate-/high-intensity statin therapy[4,5]
- Given that BA acts through the same pathway as statins, large scale safety and efficacy data for BA as an adjunct to statin therapy are needed

BA, bempedoic acid; LDL-C, low-density lipoprotein cholesterol.

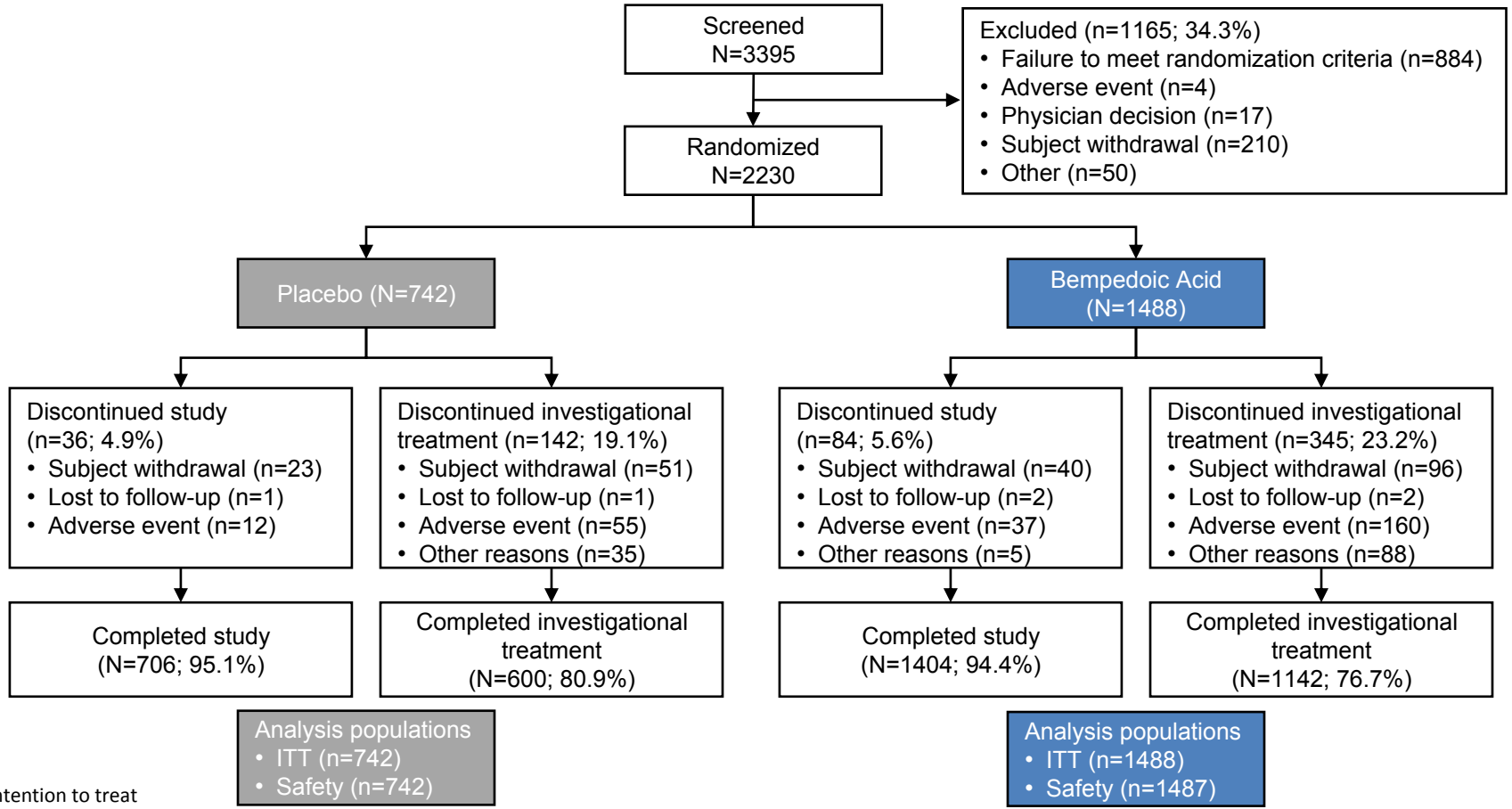
1. Thompson PD, et al. *J Clin Lipidol*. 2016;7:556-67; 2. Ballantyne CM, et al. *J Am Coll Cardiol.* 2013;62:1154-62; 3. Ballantyne CM, et al. *Am J Cardiol*. 2016;117:1928-33; 4. Stone NJ, et al. *Circulation*. 2014;129:S1-45; 5. Catapano AL, *Eur Heart J*. 2016;37:2999-3058.

CLEAR Harmony: Study Design

- Aim: Assess long-term overall safety and efficacy of BA in patients receiving maximally tolerated statin therapy
- Methods
  - Phase 3, double-blind, placebo-controlled, parallel-group study
  - Patients randomized 2:1 to treatment with BA 180 mg or placebo OD for 52 weeks
  - Key inclusion criteria
    - Pre-existing ASCVD and/or HeFH
    - Baseline LDL-C ≥ 1.8 mmol/L (70 mg/dL) while receiving maximally tolerated statin therapy
- Endpoints
  - Primary endpoint was safety
    - *P* values for safety endpoints were calculated *post hoc* and without adjustment for multiplicity
  - Principle efficacy endpoint: percent change from baseline to week 12 in LDL-C
  - Key secondary endpoints: percent change from baseline to week 24 in LDL-C, and to week 12 in non–HDL-C, total cholesterol, apoB, and hsCRP

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; OD, once daily.

CLEAR Harmony: Patient Disposition



ITT, intention to treat

CLEAR Harmony: Baseline Characteristics

Characteristic	Placebo (n=742)	BA (n=1488)
Age, years*	66.8 (8.6)	65.8 (9.1)
Male sex, %	71.3	73.9
CV risk factor, %		
Pre-existing ASCVD	98.0	97.4
HeFH	3.1	3.8
Diabetes	28.6	28.6
Hypertension	80.1	78.9
Concomitant LMT, %		
Statin	100	99.8
Ezetimibe	7.5	7.8
Fibrate	3.5	3.6
None	0	0.1

Characteristic	Placebo (n=742)	BA (n=1488)
Statin intensity, %		
Low	6.5	6.7
Moderate	43.7	43.4
High	49.9	49.9
Baseline lipids, mmol/L*		
Total cholesterol	4.63 (0.92)	4.66 (0.91)
LDL-C	2.65 (0.78)	2.68 (0.75)
Non–HDL-C	3.35 (0.88)	3.39 (0.87)
HDL-C	1.28 (0.30)	1.26 (0.31)
ApoB, mg/dL*	86.8 (21.8)	88.5 (21.6)
hsCRP, mg/dL*	1.51 (0.79–3.33)	1.49 (0.74–3.28)

*Data are means (standard deviations), except high-sensitivity C-reactive protein (hsCRP) values, which are medians (interquartile ranges).
ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy.

CLEAR Harmony: Safety (Primary Endpoint)

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Any AE	78.7	78.5	NS
Serious AE	14.0	14.5	NS
AE leading to discontinuation of study drug	7.1	10.9	0.005

*Includes adverse events (AEs) occurring from the first dose through 30 days after the last dose of study drug.
†*P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).

The difference in discontinuation frequency was not driven by any single system organ class or preferred term

CLEAR Harmony: SAEs by System Organ Class

Variable	Patients, %	
	Placebo (n=742)	BA (n=1487)
Cardiac disorders	5.7	5.2
Infections & infestations	1.5	2.6
Nervous system disorders	1.6	1.7
Vascular disorders	1.6	0.8
General disorders & administration site conditions	1.3	1.0
Neoplasms*	0.9	1.2
Gastrointestinal disorders	1.1	1.0
Injury, poisoning & procedural complications	0.9	1.1
Respiratory, thoracic & mediastinal disorders	0.4	0.9
Musculoskeletal & connective tissue disorders	0.7	0.8

Variable	Patients, %	
	Placebo (n=742)	BA (n=1488)
Renal & urinary disorders	0.5	0.4
Hepatobiliary disorders	0.3	0.5
Metabolism & nutrition disorders	0.5	0.3
Reproductive system & breast disorders	0.1	0.5
Blood & lymphatic system disorders	0.1	0.1
Eye disorders	0.1	0.1
Psychiatric disorders	0.1	0.1
Congenital, familial & genetic disorders	0	0.1
Endocrine disorders	0	0.1
Immune system disorders	0	0.1
Investigations	0	0.1

BA, bempedoic acid; SAE, serious adverse event. *Benign, malignant and unspecified (including cysts and polyps)

CLEAR Harmony: AEs of Special Interest

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Muscular disorders	10.1	13.1	NS
Leading to discontinuation of study drug	1.9	2.1	NS
Myalgia	6.1	6.0	NS
Muscle spasms	2.7	4.2	NS
Pain in extremity	2.2	3.4	NS
Muscular weakness	0.5	0.6	NS
New-onset or worsening diabetes	5.4	3.3	0.02
Gout	0.3	1.2	0.03
Blood creatinine increased	0.4	0.8	NS
Glomerular filtration rate decreased	0	0.5	NS
Neurocognitive disorders	0.9	0.7	NS

*Includes adverse events (AEs) occurring from the first dose through 30 days after the last dose of study drug.
†*P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).

CLEAR Harmony: Laboratory Results

Variable	Placebo (n=742)	Bempedoic Acid (n=1487)	*P* value*
Patients with ALT and/or AST >3 × ULN†, %	0.1	0.5	NS
Patients with creatine kinase >5 × ULN†, %	0.1	0.5	NS
Change from baseline in uric acid, mg/dL‡	–0.06 (0.87)	0.73 (1.11)	< .001

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
**P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).
†Includes elevations of greater than 3 (aminotransferase) or 5 (creatine kinase) times the upper limit of normal (ULN) that have been repeated and confirmed.
‡Data are mean changes (standard deviations) from baseline to week 52 for 680 patients in the placebo group and 1358 patients in the bempedoic acid group.

CLEAR Harmony: AEs by Statin Intensity

	Patients, %					
	Low-intensity Statin		Moderate-intensity Statin		High-intensity Statin	
Variable	Placebo (n=47)	BA (n=99)	Placebo (n=327)	BA (n=652)	Placebo (n=368)	BA (n=736)
Any AE	78.7	80.8	79.2	78.7	78.3	78.0
Serious AE	10.6	15.2	14.1	13.7	14.4	15.2
Muscle-related AE*	17.0	22.2	11.0	12.9	8.4	12.1
Common AEs†						
Nasopharyngitis	10.6	8.1	12.8	9.0	10.9	10.7
Myalgia	12.8	11.1	6.7	6.6	4.6	4.8
UTI	8.5	11.1	6.4	4.1	6.0	4.5
Pain in extremity	2.1	8.1	2.4	3.5	1.9	2.6
Dizziness	6.4	5.1	4.9	4.6	3.3	4.1
Arthralgia	2.1	5.1	7.0‡	3.8‡	5.4	4.8
URTI	2.1	2.0	2.8	3.1	5.7	6.8
Fatigue	6.4	5.1	5.2‡	2.6‡	1.4	2.2

AE, adverse event; BA, bempedoic acid; URTI, upper respiratory tract infection; UTI, urinary tract infection.
*Muscle-related adverse events were predefined as muscle spasms, myalgia, muscular weakness, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinemia, myoglinuria, myopathy, myopathy toxic, muscle necrosis, necrotizing myositis, pain in extremity, and rhabdomyolysis.
†Treatment-emergent AEs reported by at least 6% of patients in any treatment and statin intensity subgroup.
‡*P*=0.04 for the comparison of event rates in the bempedoic acid and placebo groups.

CLEAR Harmony: Adjudicated Clinical Events

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Adjudicated Clinical Events	5.7	4.6	NS
Adjudicated MACE			
Cardiovascular death	0.1	0.4	NS
Non-fatal myocardial infarction	1.8	1.3	NS
Non-fatal stroke	0.3	0.3	NS
Coronary revascularization	3.2	2.6	NS
Hospitalization for unstable angina	1.5	0.9	NS
Other MACE-related events			
Non-cardiovascular death	0.1	0.1	NS
Non-coronary arterial revascularization	0.8	0.3	NS
Hospitalization for heart failure	0.1	0.6	NS

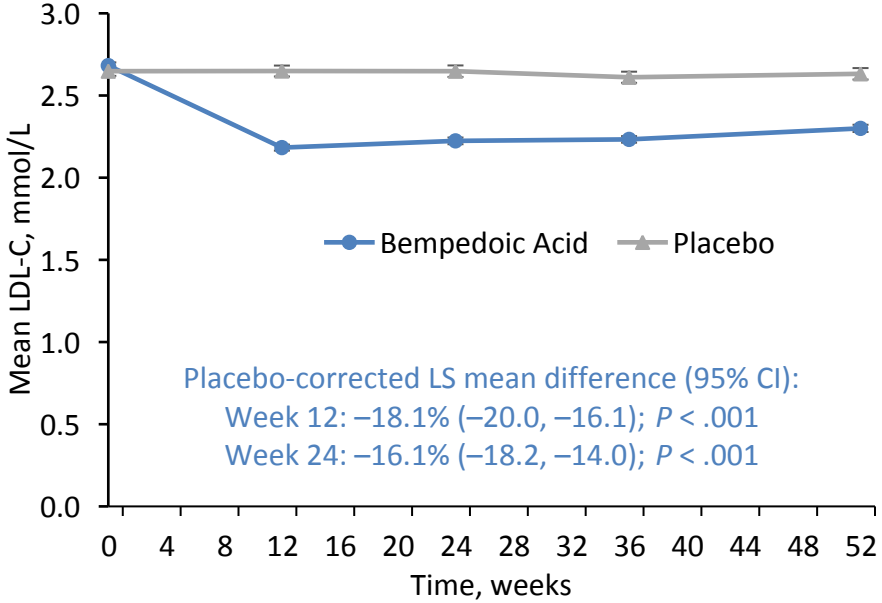
MACE, major adverse cardiac event.

*Includes adverse events (AEs) occurring from the first dose through 30 days after the last dose of study drug.

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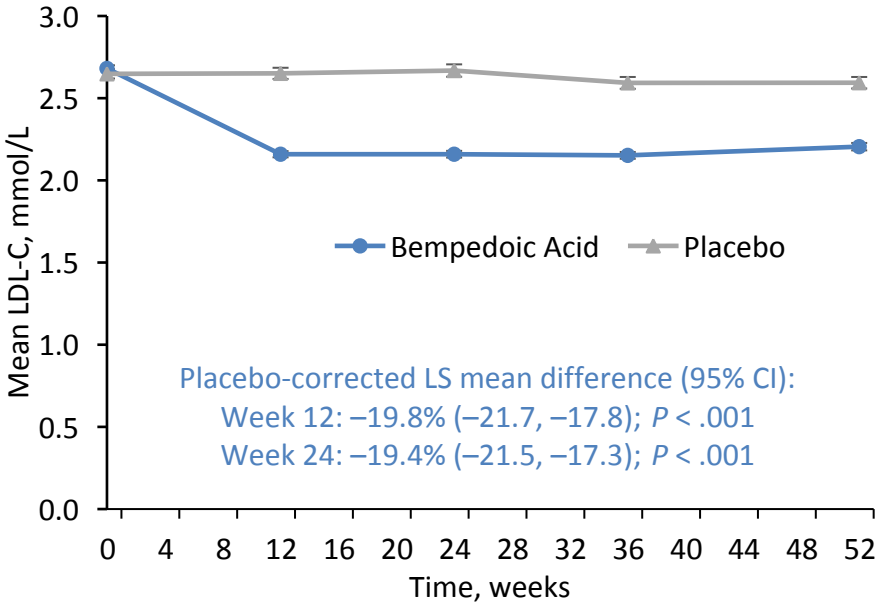
CLEAR Harmony: Percent Change in LDL-C

ITT Analysis



BA, n	1488	1424	1397	1375	1364
Placebo, n	742	725	707	692	685

On-Treatment Analysis

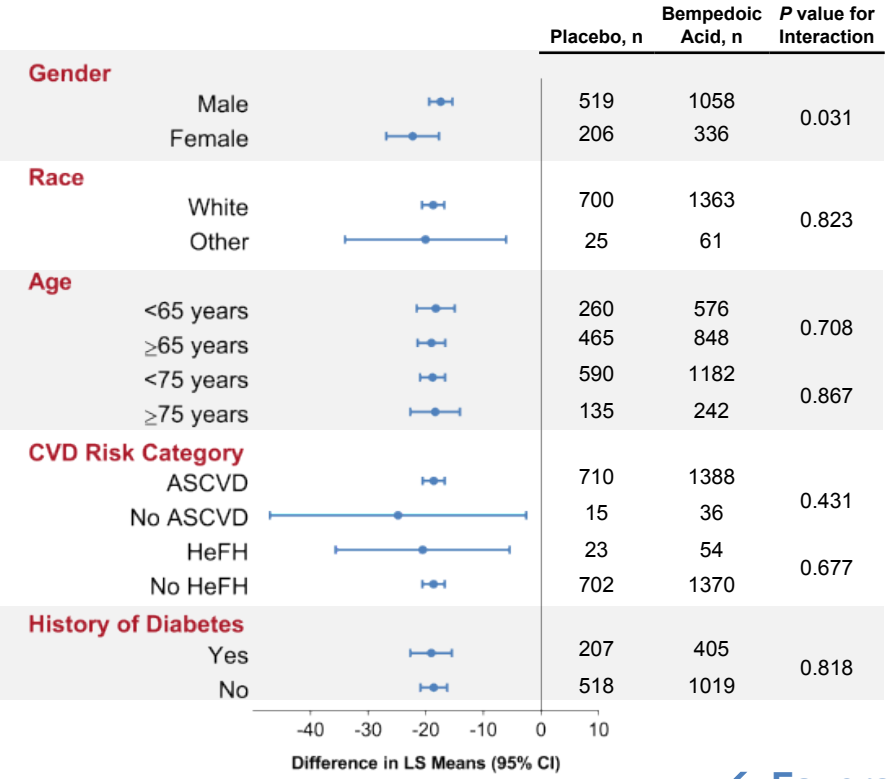


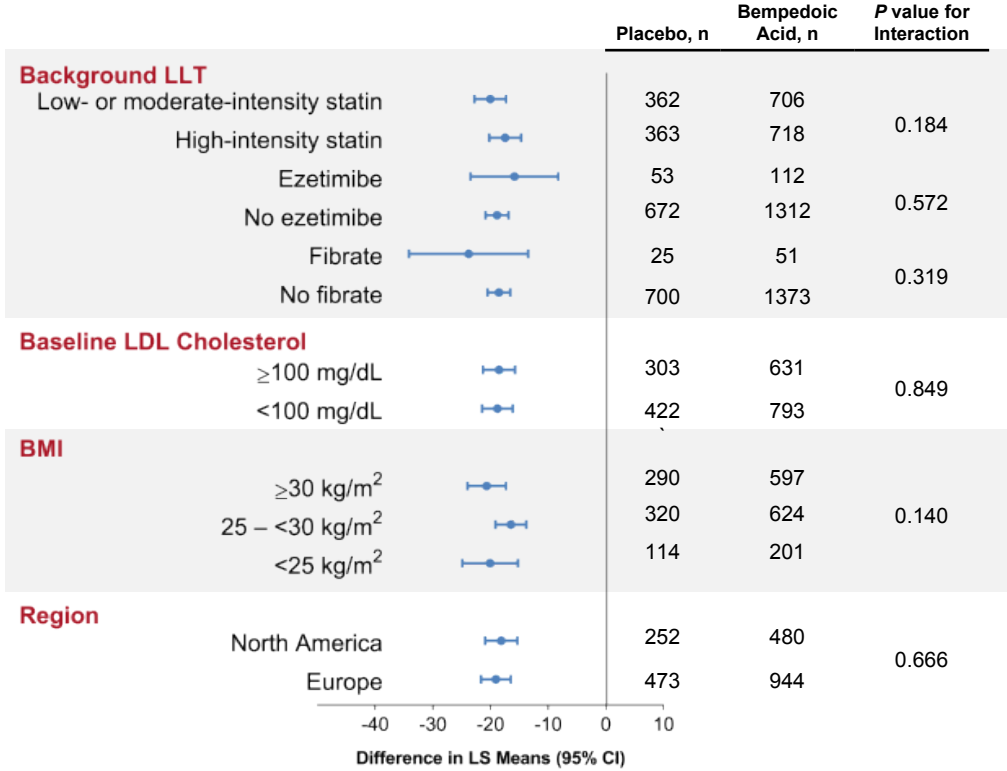
BA, n	1487	1335	1213	1172	1121
Placebo, n	742	695	643	617	589

BA, bempedoic acid; CI, confidence interval; ITT, intention to treat; LDL-C, low-density lipoprotein cholesterol. Data are least-squares (LS) means ± standard errors.

CLEAR Harmony: LDL-C Reduction by Subgroup

Percent Change from Baseline to Week 12





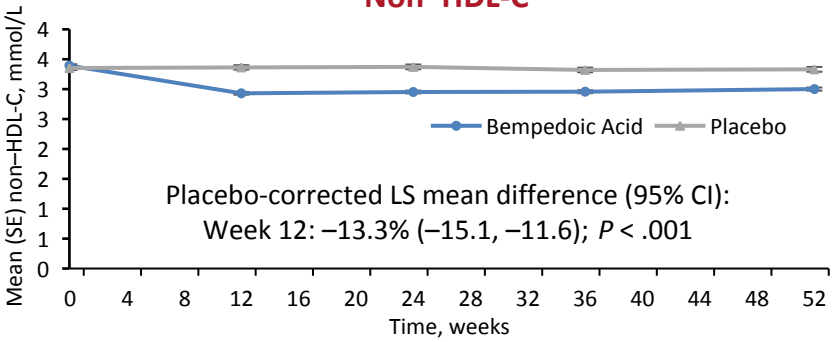
← Favors Bempedoic Acid

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ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

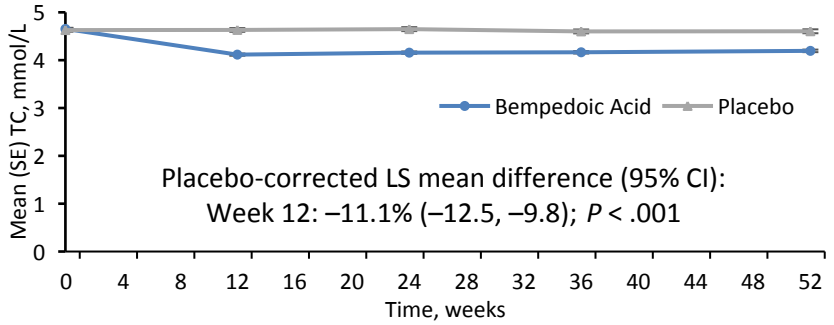
CLEAR Harmony: Secondary Efficacy Parameters

Non–HDL-C



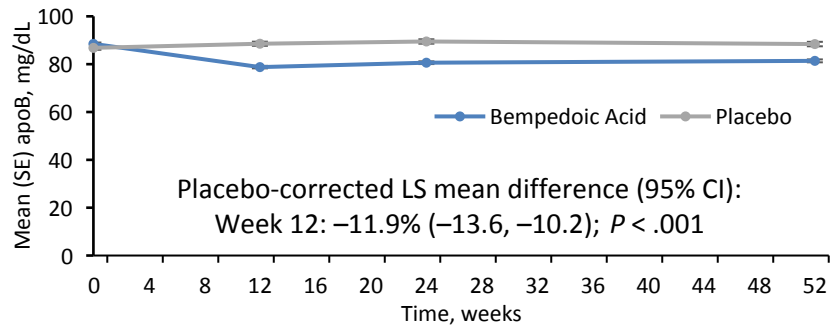
BA, n	1488	1427	1396	1375	1364
Placebo, n	742	726	707	692	685

Total Cholesterol



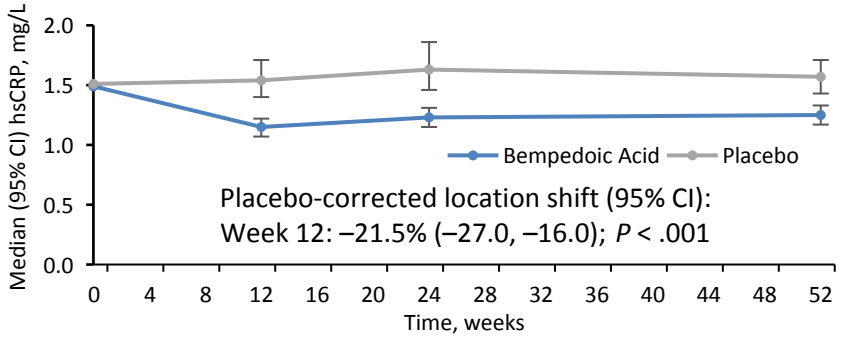
BA, n	1488	1427	1396	1375	1365
Placebo, n	742	726	708	692	685

Apolipoprotein B



BA, n	1485	1418	1384	1345
Placebo, n	736	723	704	680

hsCRP



BA, n	1487	1422	1393	1359
Placebo, n	739	726	708	683

apoB, apolipoprotein B; BA, bempedoic acid; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; LS, least-squares; non–HDL-C, non–high-density lipoprotein cholesterol; TC, total cholesterol.

Conclusions

- CLEAR Harmony provides the largest evidence to date that BA is safe as an adjunct to a guideline-based statin regimen
  - Adverse event profile of BA was generally similar to that of placebo
  - Background statin intensity did not influence the safety profile of BA
- BA reduced LDL-C at week 12 by 18.1% (ITT) and 19.8% (on-treatment)
  - Significant reductions in LDL-C were observed through to week 52
  - BA also significantly lowered non–HDL-C, total cholesterol, apoB, and hsCRP
- BA provides an additional therapeutic option to safely lower LDL-C in high ASCVD risk patients treated with statins

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol.