Phase 3 Evaluation of Bempedoic Acid Added to Ezetimibe in Patients with Elevated LDL-Cholesterol Receiving No Greater Than Low Dose Statins: CLEAR Tranquility

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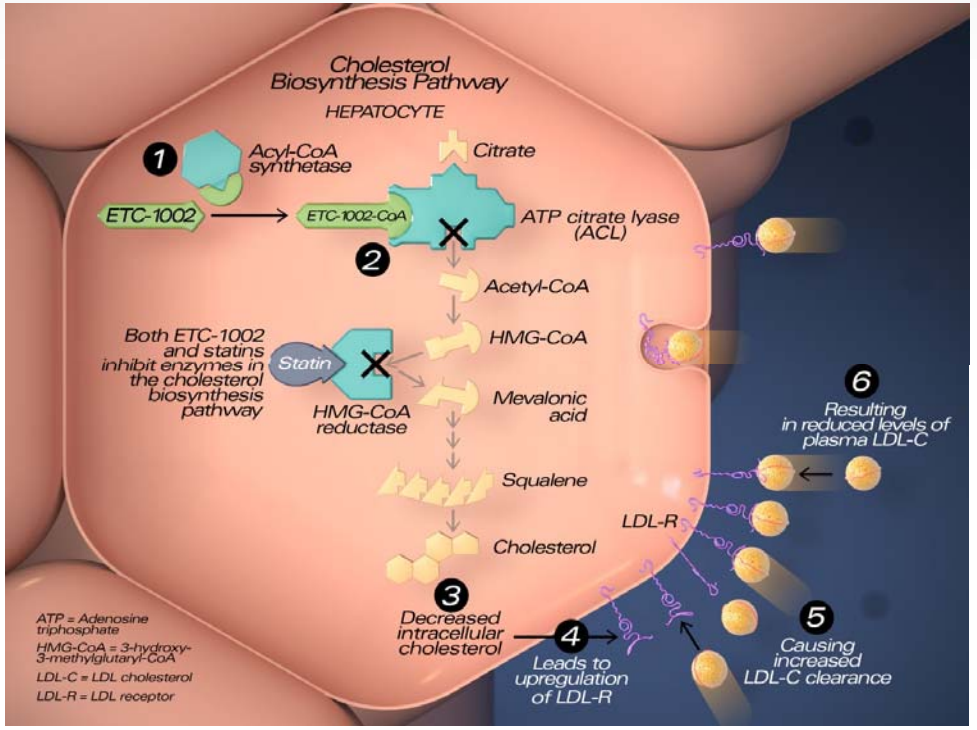
Bempedoic Acid Overview

Pharmacologic properties and Mechanism of action

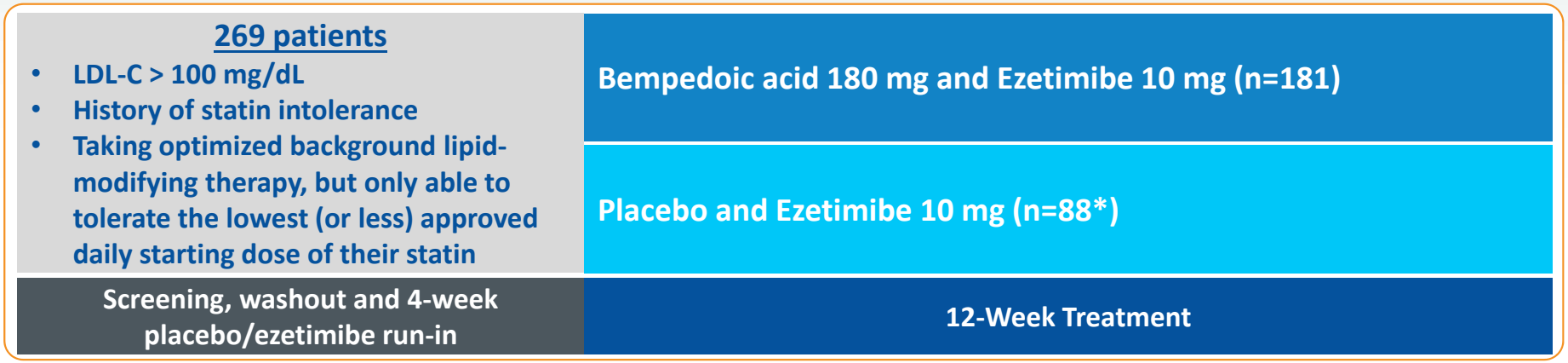
- Oral, once-daily tablet
- MOA: First-in class inhibitor of ATP-citrate lyase (ACL)
- Shown in phase 2 studies to lower LDL-C:
  - as monotherapy
  - in combination with ezetimibe, statins and PCSK9 inhibitors
  - in a broad mix of primary and secondary prevention populations



Bempedoic acid (ETC-1002) is converted by the enzyme ACSVL1 in the liver to ETC-1002-CoA which directly inhibits ACL, reduces cholesterol synthesis, and up-regulates LDL receptor activity

Study Design and Objectives

Hypothesis: Bempedoic acid will provide additional LDL-C lowering compared to placebo when added to ezetimibe in patients with a history of statin intolerance



*1 patient randomized, but did not receive study drug

Statin intolerance = history of inability to tolerate at least one statin that started with statin use and resolved upon discontinuation

Primary Objective

- LDL-C lowering efficacy of bempedoic acid versus placebo

Secondary Objectives

- Reduction of other lipids and hsCRP
- Safety and tolerability

Study conducted at 90 sites in the US, Canada and Europe

Patient Demographics

	Placebo N=88	Bempedoic Acid N=181
Demographics		
Age: Years	64 ± 11	64 ± 11
Gender: % Female (F/M)	64% (56F/32M)	60% (109F/72M)
Race, Caucasian: % (n)	85% (75)	91% (165)
Ethnicity, Hispanic or Latino: % (n)	26% (23)	24% (43)
History of ASCVD: % (n)	24% (21)	24% (44)
History of diabetes: % (n)	19% (17)	19% (35)
History of hypertension: % (n)	58% (51)	61% (111)
Taking concomitant statin background therapy*: % (n)	28% (25)	33% (59)
Intent-to-treat population, Mean ± SD, unless otherwise indicated		

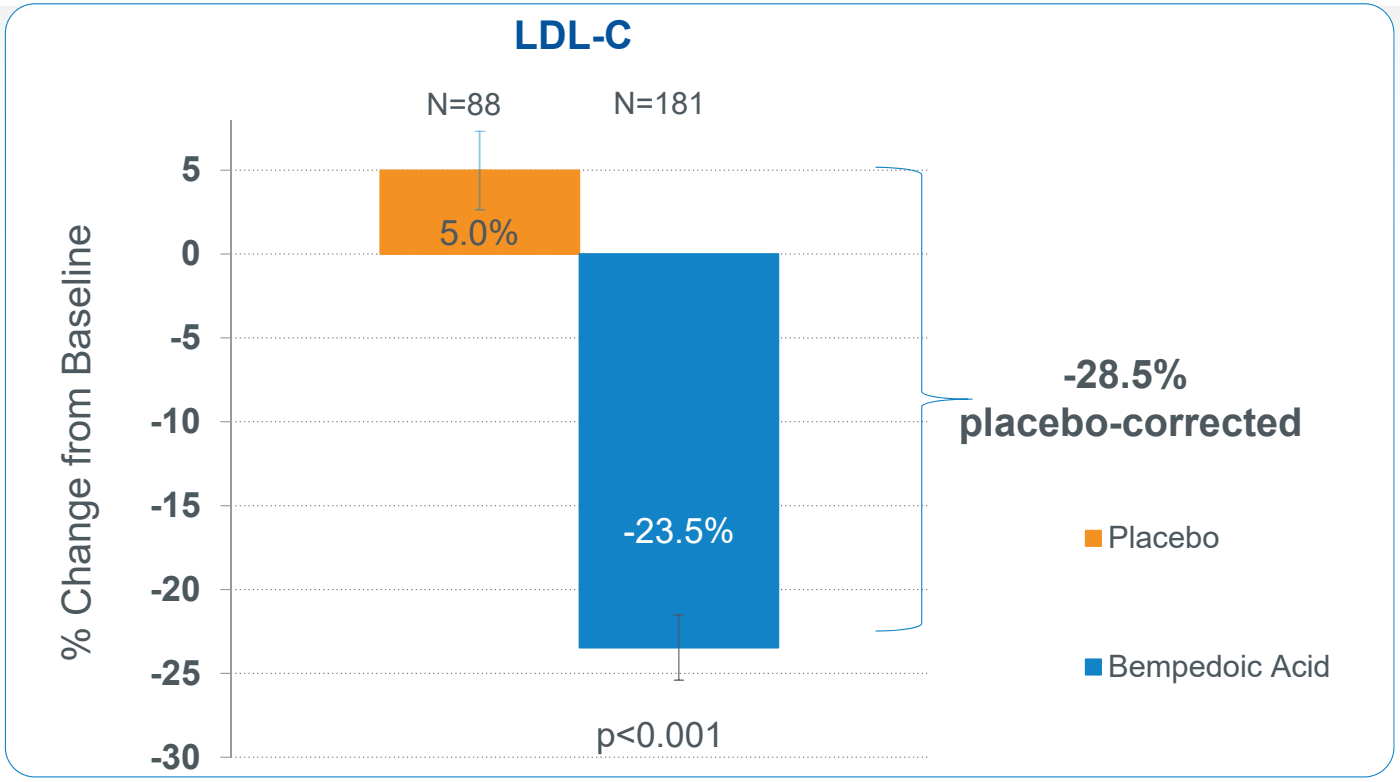
*Statin background therapies included no greater than average daily dose of atorvastatin 10 mg, fluvastatin 40 mg, lovastatin 20 mg, pitavastatin 2 mg, pravastatin 40 mg, rosuvastatin 5 mg, simvastatin 10 mg

Baseline Characteristics

	Placebo N=88	Bempedoic Acid N=181
Baseline Characteristics		
LDL-C: mg/dL	123 ± 27	130 ± 31
Non-HDL-C: mg/dL	152 ± 33	162 ± 35
Total cholesterol: mg/dL	209 ± 36	218 ± 36
Apolipoprotein B: mg/dL	116 ± 23	123 ± 26
Triglycerides: mg/dL	143 ± 62	167 ± 76
HDL-C: mg/dL	57 ± 21	56 ± 16
hsCRP[a]: mg/L	2.3 (1.1, 4.5)	2.2 (1.1, 4.0)
BMI: kg/m^2	30 ± 6	30 ± 5

Intent-to-treat population, Mean ± SD, unless otherwise indicated
[a] Median (Q1, Q3) values

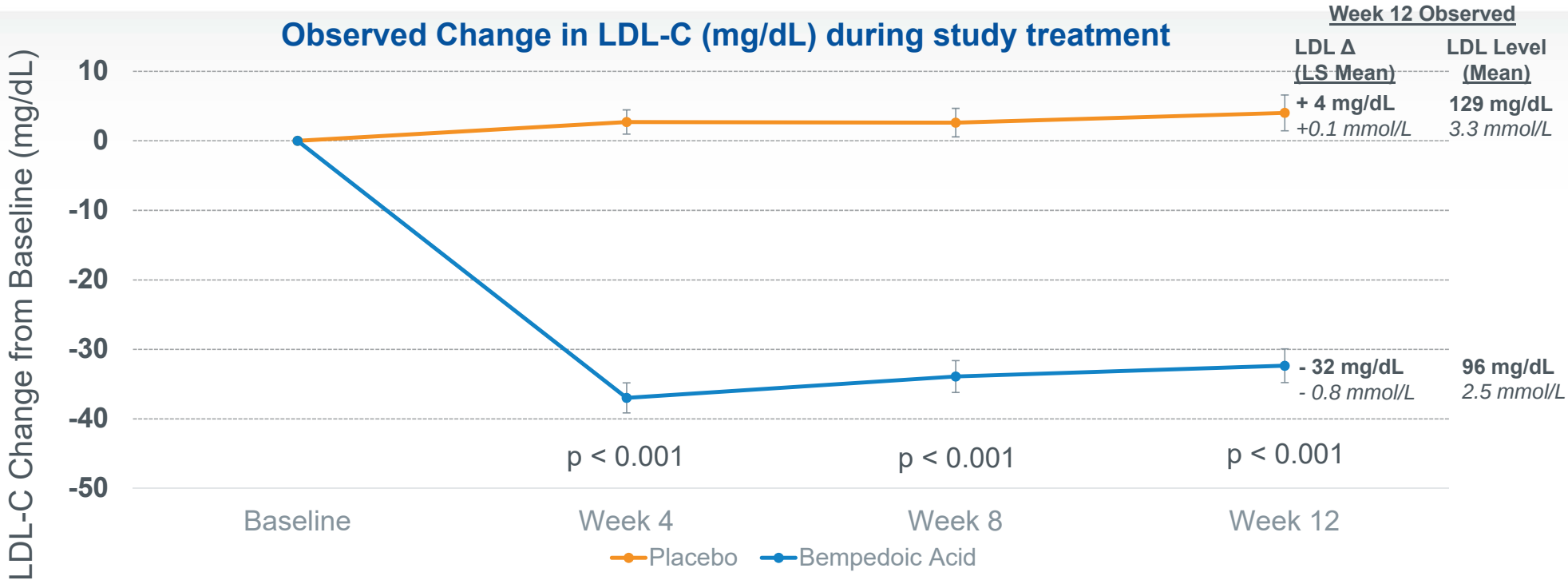
Primary Efficacy Endpoint
LDL-C Lowering at Week 12



Baseline LDL-C (mean ± SD, mg/dL)	**123 ± 27**	**130 ± 31**

Intent-to-treat (all randomized patients) population; LS Mean (SE) % change from baseline to Week 12; p-value vs. placebo by analysis of covariance model with treatment group as a factor and baseline value as covariate.

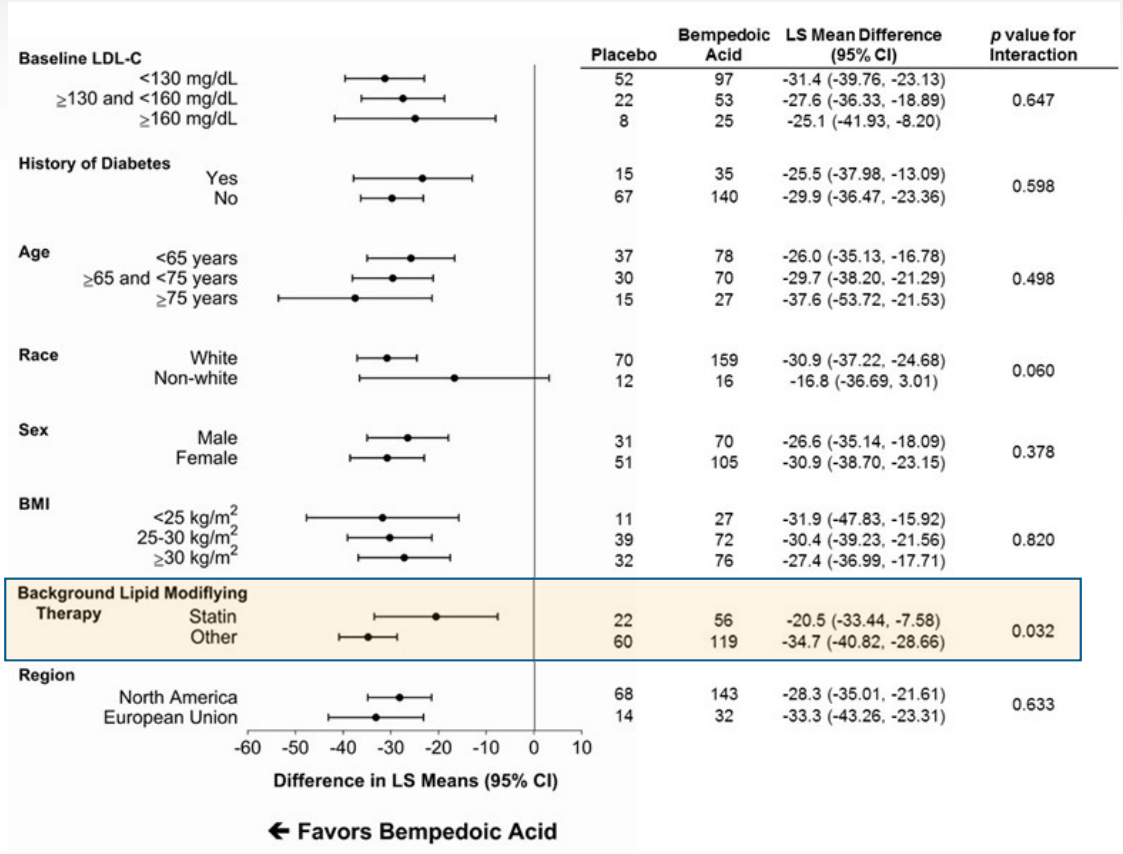
LDL-C Absolute Change from Baseline Over Time



Placebo	N=88	N=85	N=82	N=82
Bempedoic Acid	N=181	N=180	N=173	N=175

Observed least square (LS) mean ± standard error (SE) LDL-C change from baseline (mg/dL) by study visit; p-value vs. placebo by analysis of covariance model with change from baseline as dependent variable, treatment as a fixed effects and baseline as a covariate. Values for observed LDL-C LS mean change from baseline to Week 12 (Δ) and mean Week 12 LDL-C levels are presented at the right.

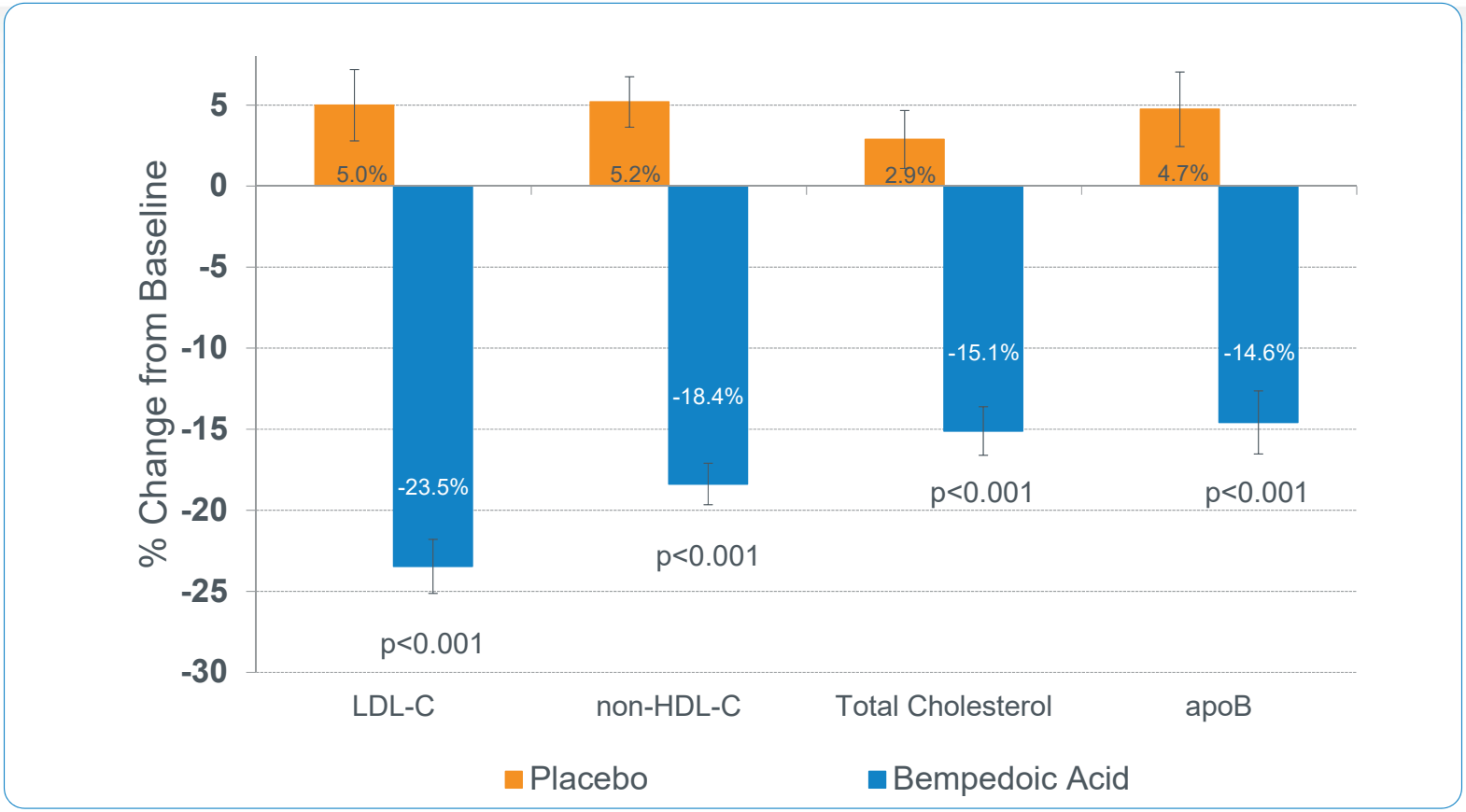
LDL-C Lowering in Subgroup Populations



	Placebo	Bempedoic Acid	LS Mean Difference (95% CI)	*p* value for Interaction
Baseline LDL-C				
<130 mg/dL	52	97	-31.4 (-39.76, -23.13)	
≥130 and <160 mg/dL	22	53	-27.6 (-36.33, -18.89)	0.647
≥160 mg/dL	8	25	-25.1 (-41.93, -8.20)	
History of Diabetes				
Yes	15	35	-25.5 (-37.98, -13.09)	0.598
No	67	140	-29.9 (-36.47, -23.36)	
Age				
<65 years	37	78	-26.0 (-35.13, -16.78)	
≥65 and <75 years	30	70	-29.7 (-38.20, -21.29)	0.498
≥75 years	15	27	-37.6 (-53.72, -21.53)	
Race				
White	70	159	-30.9 (-37.22, -24.68)	0.060
Non-white	12	16	-16.8 (-36.69, 3.01)	
Sex				
Male	31	70	-26.6 (-35.14, -18.09)	0.378
Female	51	105	-30.9 (-38.70, -23.15)	
BMI				
<25 kg/m^2	11	27	-31.9 (-47.83, -15.92)	
25-30 kg/m^2	39	72	-30.4 (-39.23, -21.56)	0.820
≥30 kg/m^2	32	76	-27.4 (-36.99, -17.71)	
Background Lipid Modifying Therapy				
Statin	22	56	-20.5 (-33.44, -7.58)	0.032
Other	60	119	-34.7 (-40.82, -28.66)	
Region				
North America	68	143	-28.3 (-35.01, -21.61)	0.633
European Union	14	32	-33.3 (-43.26, -23.31)	

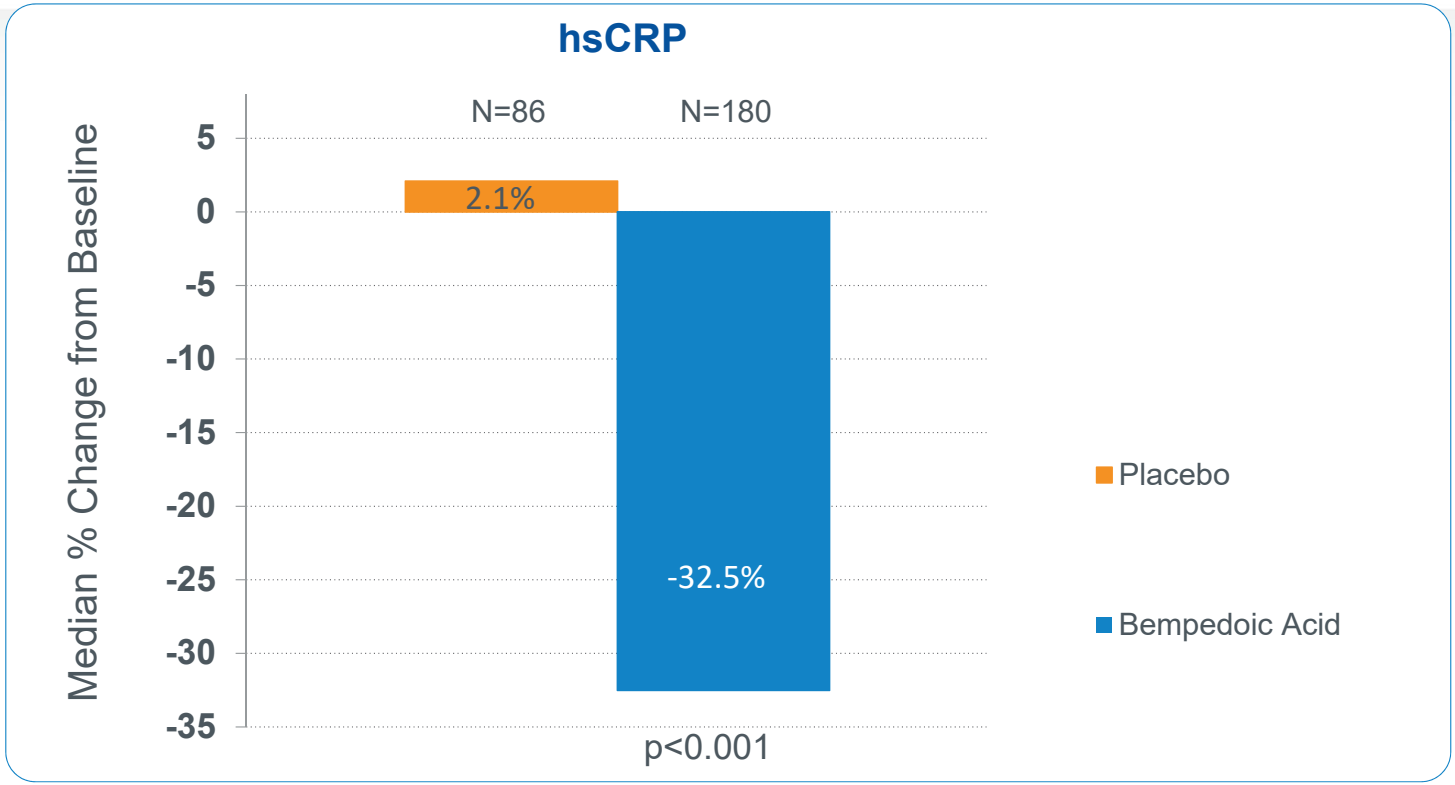
Subgroup analysis of intent-to-treat population; LS Mean (SE) % change from baseline to Week 12; p-value vs. placebo by analysis of covariance model. Subpopulation sample size shown under treatment arm.

Secondary Efficacy Endpoints
Effect on Other Lipid Parameters at Week 12



Intent-to-treat (all randomized patients) population; LS Mean (SE) % change from baseline to Week 12; p-value vs. placebo by analysis of covariance model with treatment group as a factor and baseline value as covariate.

Secondary Efficacy Endpoint
Reduction in hsCRP at Week 12



Baseline hsCRP (median, mg/L)	**2.3**	**2.2**

Intent-to-treat (all randomized patients) population; Median % change from baseline to Week 12; p-value vs. placebo by Wilcoxon rank-sum model (non-parametric).

Safety and Tolerability: Overall TEAEs

Treatment Emergent Adverse Events (AEs)	% (Number) of Patients	
	Placebo N=87	Bempedoic Acid N=181
Overview of Treatment Emergent AEs in All Patients		
Any AE(s)	44.8% (39)	48.6% (88)
Serious AE(s)	3.4% (3)	2.8% (5)
IMP discontinued due to AE(s)	5.7% (5)	6.1% (11)
Fatal AE(s)	0% (0)	0% (0)

Safety analysis set (all patients that received at least one dose of IMP) population; Incidence of AEs; IMP = Investigational Medicinal Product (Bempedoic acid or Placebo).

Safety and Tolerability: Most Common TEAEs

Treatment Emergent Adverse Events (AEs)	% (Number) of Patients	
	Placebo N=87	Bempedoic Acid N=181
Overview of Treatment Emergent AEs in All Patients		
Any AE(s)	44.8% (39)	48.6% (88)
Treatment Emergent AEs Occurring in ≥ 2% of Patients		
Urinary tract infection	5.7% (5)	2.8% (5)
Headache	3.4% (3)	4.4% (8)
Muscle spasms	3.4% (3)	3.3% (6)
Blood uric acid increased	2.3% (2)	7.7% (14)
Myalgia	2.3% (2)	1.7% (3)
Diabetes mellitus	2.3% (2)	1.1% (2)
Vertigo	2.3% (2)	0% (0)
Vulvovaginal mycotic infection	2.3% (2)	0% (0)
Nasopharyngitis	1.1% (1)	2.2% (4)
Liver function test increased	0% (0)	3.9% (7)
Nausea	0% (0)	2.8% (5)
Sinusitis	0% (0)	2.8% (5)
Glomerular filtration rate decreased	0% (0)	2.2% (4)

Safety analysis set (all patients that received at least one dose of IMP) population; Incidence of AEs; IMP = Investigational Medicinal Product (Bempedoic acid or Placebo).

Skeletal Muscle TEAEs and Discontinuations

Muscle-related Treatment Emergent Adverse Events (AEs)	% (Number) of Patients	
	Placebo N=87	Bempedoic Acid N=181
Overview of Potential Muscle-related Treatment Emergent AEs in All Patients		
Any Potential Muscle AE(s)	5.7% (5)	6.1% (11)
IMP discontinued due to Potential Muscle AE(s)	1.1% (1)	1.1% (2)
All Potential Muscle AEs by MedDRA Preferred Term		
Muscle spasms	3.4% (3)	3.3% (6)
Myalgia	2.3% (2)	1.7% (3)
Muscular weakness	0% (0)	0.6% (1)
Pain in extremity	0% (0)	0.6% (1)

Safety analysis set (all patients that received at least one dose of IMP) population; Incidence of AEs; IMP = Investigational Medicinal Product (Bempedoic acid or Placebo). Includes all “muscular disorders” pre-defined in the Statistical Analysis Plan as often associated with statin intolerance: muscle spasms, myalgia, muscular weakness, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinaemia, myoglobinuria , myopathy, myopathy toxic, necrotizing myositis, pain in extremity, rhabdomyolysis.

Laboratory Parameters of Interest

Laboratory Abnormality (Repeated and Confirmed)	% (Number) of Patients	
	Placebo N=87	Bempedoic Acid N=181
ALT and/or AST > 3 x ULN	0% (0)	1.1% (2)
ALT and/or AST > 5 x ULN	0% (0)	0% (0)
Creatine Kinase > 5 x ULN	0% (0)	0% (0)

2 cases of ALT and/or AST > 3 x ULN repeated and confirmed

- ALT and AST were elevated above ULN prior to randomization
- LFT increased to > 3 x ULN occurred at week 8 for one patient and week 12 for other patient
- No patients experienced increases in total bilirubin > 2 x ULN
- No patients met Hy's law criteria

Safety analysis set (all patients that received at least one dose of IMP) population; Incidence of abnormal lab meeting criteria; evaluated as repeated and confirmed if repeat assessment was conducted within 7 days if IMP had been discontinued or at next assessment if IMP is ongoing. If no repeat assessment occurs it is considered repeated and confirmed.

KEY FINDINGS

- Added to background ezetimibe therapy, bempedoic acid 180 mg:
  - Significantly lowered LDL-C by -28.5% vs. placebo ($p<0.001$; -23.5% BA vs. +5.0% placebo)
    - ➢ Reduced mean LDL-C from 130 mg/dL to 96 mg/dL over the 12 week period
  - Significantly reduced non-HDL-C, total cholesterol, apoB and hsCRP ($p<0.001$)
  - Was safe and well tolerated, comparable to placebo
    - ➢ Similar frequency of treatment-emergent AEs, discontinuations, and muscle-related AEs

LIMITATIONS

- Patients who could not tolerate the placebo run-in phase were excluded prior to randomization which may contribute to the overall low incidence of muscle-related AEs reported.

- The 12-week treatment duration is a short period to fully assess safety. The long-term safety of bempedoic acid is being assessed by ongoing phase 3 clinical trials including:
  - 1 study of 24-week duration (CLEAR Serenity [NCT02988115])
  - 2 studies of 52 week duration (CLEAR Harmony [NCT02666664] and CLEAR Wisdom [NCT02991118])
  - 1 open-label extension study of 1.5-year duration [NCT03067441]
  - 1 Cardiovascular outcomes study (CLEAR Outcomes [NCT02993406])

- Compliance to background lipid therapy was not monitored, thereby precluding assessment of the influence of statin adherence on treatment response.

- Enrollment criterion of a history of statin intolerance was based on patient self-reporting which is less rigorous than a statin challenge/rechallenge approach; nevertheless represents a common scenario in practice.

CONCLUSION

Bempedoic acid may offer an additional oral therapeutic option complementary to background ezetimibe in patients with ASCVD and high risk primary prevention patients requiring additional LDL-C lowering and unable to tolerate moderate or high dose statins.

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Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study

Christie M. Ballantyne, Maciej Banach, G. B. John Mancini, Norman E. Lepor, Jeffrey C. Hanselman, Xin Zhao, Lawrence A. Leiter

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