Supplementary Appendix

Safety and Efficacy of Bempedoic Acid

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2. Study Oversight

CLEAR Harmony was designed by the sponsor, Esperion, and overseen by an academic steering committee. Data collection was executed by the investigators with assistance from ICON Clinical Research, Inc. (Dublin, Ireland) and analyzed by ICON. A blinded clinical events committee adjudicated designated clinical end points, while an independent data monitoring committee formally reviewed unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid.

2.1. Steering Committee

Member	Affiliation
Christie Ballantyne, M.D. (Chairman)	Baylor College of Medicine, Houston, TX
Maciej Banach, M.D.	University of Lodz, Lodz, PL
Harold Bays, M.D.	L-MARC Research Center, Louisville, KY
Alberico Catapano, Ph.D.	University of Milan, Milano and IRCCS Multimedica, IT
Bart Duell, M.D.	Oregon Health and Science University, Portland, OR
William Sasiela Ph.D.*	Esperion Therapeutics, Ann Arbor, MI
Anne Goldberg, M.D.	Washington University School of Medicine, St. Louis, MO
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Ulrich Laufs, M.D.	Saarland University Medical Center, Homburg, DE
Larry Leiter, M.D.	University of Toronto, Toronto, CA
John Mancini, M.D.	University of British Columbia, Vancouver, CA
Pamela Morris, M.D	Medical University of South Carolina, Charleston, SC
Kausik K. Ray, M.D., M.Phil.	Imperial College London, London, UK
Erik Stroes, M.D.	Academic Medical Center, Amsterdam, NL

*Nonvoting members

2.2 Clinical Events Adjudication Committee

All based at the Cleveland Clinic, Cleveland Ohio, USA

Venugopal Menon, M.D.

Jitendra Sharma, M.D.

Kevin Trulock, M.D.

Terence Hill, M.D.

Matthew Summers, M.D.

Kenneth Varian, M.D.

Jonathan Hansen, M.D.

Richard Meredith, M.D.

Bo Xu, M.D.

2.3 Independent Data Monitoring Committee

Name/Credentials	**Address**
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3. Trial Registration

Registration for study 1002-040 was submitted to ClinicalTrials.gov on January 19, 2016.

- The first patient was screened on January 18, 2016, and was randomized on January 28, 2016. No other patients were screened prior to study registration.
- The timing of registering the study on ClinicalTrials.gov was based on meeting legal requirements (to register within 21 days after the first patient is enrolled) rather than those of ICMJE.
- No patients were randomized prior to registration at ClinicalTrials.gov.

4. Study Methods

4.1 Inclusion Criteria

1. Age ≥18 years or legal age of majority based on regional law, whichever is greater at week 2 (visit S1).
2. Men and nonpregnant, nonlactating women. Women must be either:
    - Naturally post-menopausal (as reported by the patient), defined as older than 55 years and ≥1 year without menses, younger than 55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
    - Women of childbearing potential must be willing to use 1 acceptable method of birth control. The minimal requirement for adequate contraception is that it should be started on day 1, continuing during the study period, and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include: oral birth control medications; placement of an intrauterine device (IUD) with or without hormones; barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly; vasectomized male partner who is the sole partner for this patient; or true abstinence (not including periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods, or withdrawal).
    - There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
3. Fasting low-density lipoprotein (LDL-C) value at week –2 (visit S1) ≥70 mg/dl (1.8 mmol/L).

    Note: LDL-C testing may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat LDL-C tests, the mean of the first value and the repeat value will be used to determine eligibility.

4. Have high cardiovascular risk that is defined as either:
    - Diagnosis of heterozygous familial hypercholesterolemia (HeFH). Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points or the Simon Broome Register Diagnostic Criteria with an assessment of “Definite HeFH”. Patients with a diagnosis of HeFH may or may not have established coronary heart disease (CHD) or CHD risk equivalents.

OR

- Have atherosclerotic cardiovascular disease (ASCVD) with established CHD or CHD risk equivalents.

  Documented history of CHD (includes 1 or more of the following):

  – Acute myocardial infarction (MI)
  – Silent MI
  – Unstable angina
  – Coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)
  – Clinically significant CHD diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

  Documented CHD risk equivalents (includes 1 or more of the following criteria):

  – Peripheral arterial disease
  – Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and nonischemic neurological disease

    Note: Patients with type 2 diabetes mellitus (T2DM) are allowed in this study; however, for this study T2DM is not considered a CHD risk equivalent

5. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin either alone or in combination with other lipid-lowering therapies, at stable doses for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed). Regimens other than daily dosing, including those at very low doses, are acceptable.

   A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using his or her medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

4.2 Exclusion Criteria

1. Total fasting triglyceride (TG) ≥500 mg/dl (5.6 mmol/L) at week –2 (visit S1)

   Note: TG testing may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG test, the mean of the first value and the repeat value will be used to determine eligibility.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 ml/min/1.73 m^2 at week 2 (visit S1).

   Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR test. For those patients who have a repeat eGFR testing, the repeat value will be used to determine eligibility.

   Note: Also excluded are renally impaired patients receiving an average daily dose of simvastatin 40 mg with eGFR below <45 ml/min/1.73 m^2.

3. Body mass index (BMI) ≥50 kg/m^2.
4. Concomitant use of simvastatin at average daily doses greater than 40 mg.
5. Concomitant use of a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at week –2 (visit S1) or prior use of a PCSK9 inhibitor within the past 4 weeks of week –2 (visit S1) will be excluded from this study.

   Note: Patients are allowed to initiate a PCSK9 inhibitor as adjunctive therapy at week 24 if the LDL-C threshold criteria have been met.

6. Recent (within 3 months prior to the screening visit [week –2 (visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (e.g., PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the investigator to be stable for the previous 3 months.
7. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg after sitting quietly for 5 minutes. Note: If the

initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the investigator, the screening period may be extended up to 2 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria.

8. Hemoglobin A_{1C} (HbA_{1C}) ≥10% at week –2 (visit S1).
9. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at week –2 (visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.
10. Liver disease or dysfunction, including:
    - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at week –2 (visit S1); or
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥1.2 × ULN at week –2 (visit S1).

    Note: If HCV-AB is positive, a reflex hepatitis C virus-ribonucleic acid (HCV-RNA) test will be performed to rule out active disease. Patients without active disease may be enrolled the study.

    Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB testing. For those patients who have a repeat ALT, AST, and/or TB test, the repeat value will be used to determine eligibility.

    If TB is ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin test will be ordered and if values are consistent with Gilbert's disease, the patient may be enrolled in the study.
11. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) that may affect drug absorption.
12. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dl (100 g/l) at week –2 (visit S1).
13. Active malignancy, including those patients requiring surgery, chemotherapy, and/or radiation in the past 5 years. Patients with a history of nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.

14. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (i.e., not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK values ≤3 × ULN prior to randomization.
15. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a healthcare practitioner can be enrolled after evaluation by the investigator.
16. Blood donation, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization.
17. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer.
18. Prior participation in a previous bempedoic acid clinical study. Prior participation in a clinical study with bempedoic acid is defined as having been enrolled in a bempedoic acid study.
19. Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;
    - New or planned dose changes of systemic corticosteroids.
    - Requirement for mipomersen or lomitapide or apheresis therapy.
20. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
    - Hormone replacement (6 weeks prior to randomization).
    - Thyroid replacement (6 weeks prior to randomization).
    - Diabetes medications (4 weeks prior to randomization).
    - Obesity medication (3 months prior to randomization).
21. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or sponsor.

4.3 Baseline Statin Dose Categories.

High-intensity Statins	Moderate-intensity Statins	Low-intensity Statins*
Atorvastatin 40 – 80 mg	Atorvastatin 10 – 20 mg	Simvastatin 10 mg
Rosuvastatin 20 – 40 mg	Rosuvastatin 5 – 10 mg	Pravastatin 10 – 20 mg
	Simvastatin 20 – 40 mg	Lovastatin 20 mg
	Pravastatin 40 – 80 mg	Fluvastatin 20 – 40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg twice daily	
	Pitavastatin 2 – 4 mg	

*Low-intensity statins also include those patients taking low-dose statins using an alternate regimen (i.e., every other day or for a specified number of times per week).

4.4 Randomization Strata.

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH + low-intensity statins	ASCVD + low-intensity statins
HeFH + moderate-intensity statins	ASCVD + moderate-intensity statins
HeFH + high-intensity statins	ASCVD + high-intensity statins

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

4.5 Clinical End Point Adjudication

A blinded independent expert clinical events committee (See Section 2.2) adjudicated designated clinical end points, including all major adverse cardiac events (MACE) and non-MACE end points, defined as: cardiovascular death (MACE), noncardiovascular death (non-MACE), non-fatal myocardial infarction (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), noncoronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), using standardized definitions.

4.6 Laboratory Analytical Methods

After randomization, patients returned to the clinic every 4 weeks for the first 12 weeks, then approximately every 12–16 weeks through week 52. Clinical laboratory samples were collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers, including non–high-density lipoprotein (HDL) cholesterol, HDL cholesterol, total cholesterol,

apolipoprotein B, high-sensitivity C-reactive protein (hsCRP), and TGs at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters. All analyses were performed at a central laboratory (ICON Laboratory Services, Inc.).

LDL-C was calculated using the Friedewald equation: LDL-C in mg/dl = total cholesterol – HDL-C – (TGs ÷ 5). If TGs exceeded 400 mg/dl (4.5 mmol/L) or LDL-C was ≤50 mg/dl (1.3 mmol/L), direct measurement of LDL-C was performed using the MULTIGENT Direct LDL assay with Abbott ARCHITECT system instrumentation.

Total cholesterol and TGs were quantified using enzymatic methods and the Abbott ARCHITECT System instrumentation. The reagent for total cholesterol was developed using the formulation of Allain et al.[1] and the related modification published by Röschlau,[2] with additional improvements to enhance reagent stability. The TG analytical method was derived from that of Fossati et al[3] and McGowan et al,[4] with 4-chlorophenol substituted for 2 -hydroxy-3,5-dichlorobenzenesulfonate.

Non–HDL-C was calculated by subtracting HDL-C from total cholesterol. HDL-C was quantified using the Ultra HDL assay and analyzed on the Abbott ARCHITECT system.

Apolipoprotein B was quantified via immunonephelometry using Siemens Healthcare Diagnostics BN II instrumentation. hsCRP levels were measured using the MULTIGENT CRP Vario immunoassay and the Abbott ARCHITECT system.

4.7 Sample Size

The table below provides a quantitative illustration of the sample size determination. Assuming the placebo adverse event rates observed in the current study are similar to those observed in a prior long-term trial of lipid-lowering therapy conducted in a similar patient population,[5] a range of possible adverse rates were selected, with relative risks and associated confidence intervals calculated for illustration purposes. Note that because the primary end point is general safety, the safety objective is assessed via the overall safety profile rather than limiting the analysis to any imbalance, or lack thereof, between treatment groups for any single event.

Hypothesized AE Rate in the Placebo Group	Hypothesized AE Rate in the Bempedoic Acid Group	Relative Risk	Approximate 95% CI for Relative Risk
0.5%	0.5%	1.0	(0.3, 3.8)
1.6%	1.6%	1.0	(0.48, 2.09)
13.6%	13.6%	1.0	(0.8, 1.3)
0.5%	1.0%	2.0	(0.6, 6.7)
1.6%	3.2%	2.0	(1.02, 3.92)
13.6%	27.2%	2.0	(1.6, 2.5)

AE, adverse event; CI, confidence interval.

4.8 Statistical Analyses – Efficacy End Points

Baseline Definition

Baseline for fasting lipid parameters including LDL-C, total cholesterol, HDL cholesterol, non-HDL cholesterol, and TGs is defined as the average of the last 2 nonmissing values on or prior to study day 1. If only 1 value is available, the single value is used as baseline. For other parameters, including apolipoprotein B and hsCRP, baseline is defined as the last nonmissing value/result on or prior to study day 1, unless otherwise specified.

Primary Efficacy End Points and Analyses

For all efficacy analyses, the intention-to-treat (ITT) population was used, with patients included in their randomized group, regardless of the treatment they actually received.

The primary and key secondary efficacy end points were included in a step-down testing procedure to control overall type I error. End points listed below were tested sequentially at an alpha level of 0.05. Each end point was tested only if the previous end point achieved statistical significance.

1. Percent change from baseline to week 12 in LDL-C (primary efficacy).
2. Percent change from baseline to week 24 in LDL-C.
3. Percent change from baseline to week 12 in non-HDL-C.
4. Percent change from baseline to week 12 in total cholesterol.
5. Percent change from baseline to week 12 in apolipoprotein B.
6. Percent change from baseline to week 12 in hsCRP.

The clinical hypothesis tested for each respective end point is that a treatment regimen with bempedoic acid 180 mg daily in addition to other lipid-modifying therapies (including statins)

will result in higher reduction in respective lipid value than that from the lipid modifying therapy alone.

Percent change in LDL-C, non-HDL-C, total cholesterol, and apolipoprotein B at week 12 or week 24 were analyzed using the analysis of covariance (ANCOVA) method. The ANCOVA model included treatment and randomization stratum as factors, and baseline value as a covariate. In case the number of subjects within a stratum was too small for a meaningful analysis, the strata were combined to obtain larger cell size. To account for the likelihood of unequal variances between the treatment groups, the ANCOVA model was implemented within mixed-model framework and the <repeated/group=> option was used to allow estimating the residual variances separately between the groups. The model assumptions for ANCOVA were assessed and if these assumptions were severely violated, an alternative nonparametric approach was performed.

For hsCRP, a nonparametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval was performed because, based on historical knowledge, publication precedence,[6] and recent data available, hsCRP is known to be skewed by extreme values and have non-normal distribution.

Missing Data Imputation

Missing data for efficacy end points included in the step-down procedure were imputed using a pattern-mixture model (PMM) to specify different imputation strategies depending on whether the patient was still on study treatment. Patients with missing lipid data at week 12 who were no longer taking study treatment (date of last dose of study drug was < week 12 visit date – 7) were assumed to no longer be benefitting from study drug, and their missing value(s) were assumed to be similar to those from the placebo patients who have data. To account for uncertainty, missing values were imputed using multiple imputation via a regression-based model including stratification factor, baseline value and week 12 value using data from placebo patients only. In this imputation model, treatment group was not included as a factor.

Patients with missing lipid data at week 12 who were still taking study treatment (date of last dose of study drug is ≥ date of week 12 visit – 7) were assumed to continue to benefit from study drug, and their missing value(s) were assumed to be similar to those who remain on study treatment and have data. As a result, missing lipid values were imputed based on the observed values in their randomized treatment group. To account for uncertainty, missing values were

imputed using multiple imputation via a regression-based model including data from both treatment groups. In this imputation model, treatment group was included as a factor.

Subgroup Analysis

Percent change from baseline in LDL cholesterol at week 12 was analyzed within subgroups without imputation for missing data. Subgroups included:

- Gender (male vs. female).
- Age (< 65 years vs. ≥65 years and <75 years vs. ≥75 years).
- Baseline cardiovascular disease risk category (ASCVD vs. no ASCVD and HeFH vs. no HeFH).
- Baseline statin intensity (low or moderate vs. high).
- Baseline nonstatin lipid-lowering therapy (ezetimibe vs nonezetimibe and fibrate vs non-fibrate).
- Race (White vs. other)
- Baseline LDL category (<100 mg/dl vs. ≥100 mg/dl).
- History of diabetes (yes vs. no).
- Body mass index (<25, 25 to <30, ≥30 kg/m^2).
- Region (North America, Europe).

Sensitivity Analyses

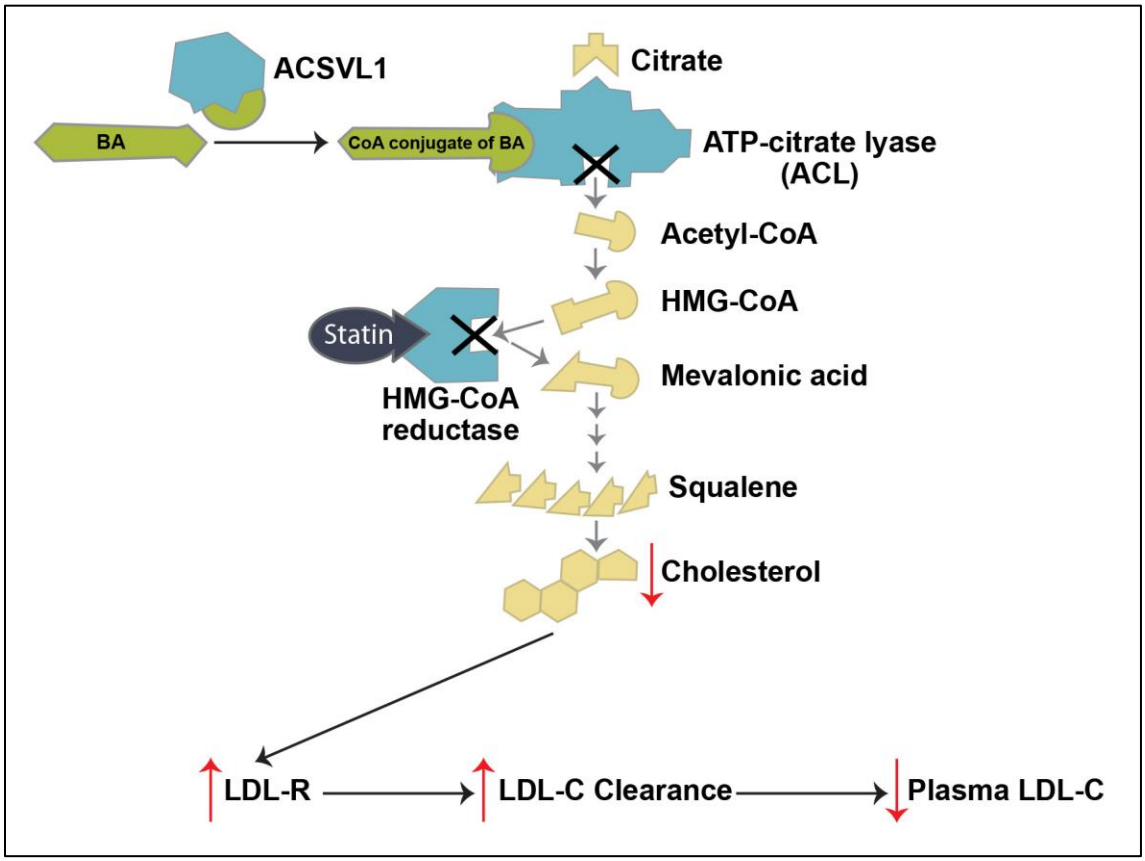
Sensitivity analyses were performed as follows:

- Sensitivity analyses for primary and key secondary end points included in the step-down procedure were performed using the ANCOVA model with derived stratum instead of randomized stratum.
- Observed case data only (no imputations for missing data) were used for sensitivity analyses of primary and key secondary end points. Observed data analysis were conducted using the ITT population.
- On-treatment analyses were conducted using data collected during the treatment period only (i.e., up to the date of last dose of study drug + 7 days; any efficacy data collected after 7 days post last dose of study drug was excluded for efficacy analysis). On-treatment analyses were conducted using the safety population for primary and key secondary end points.

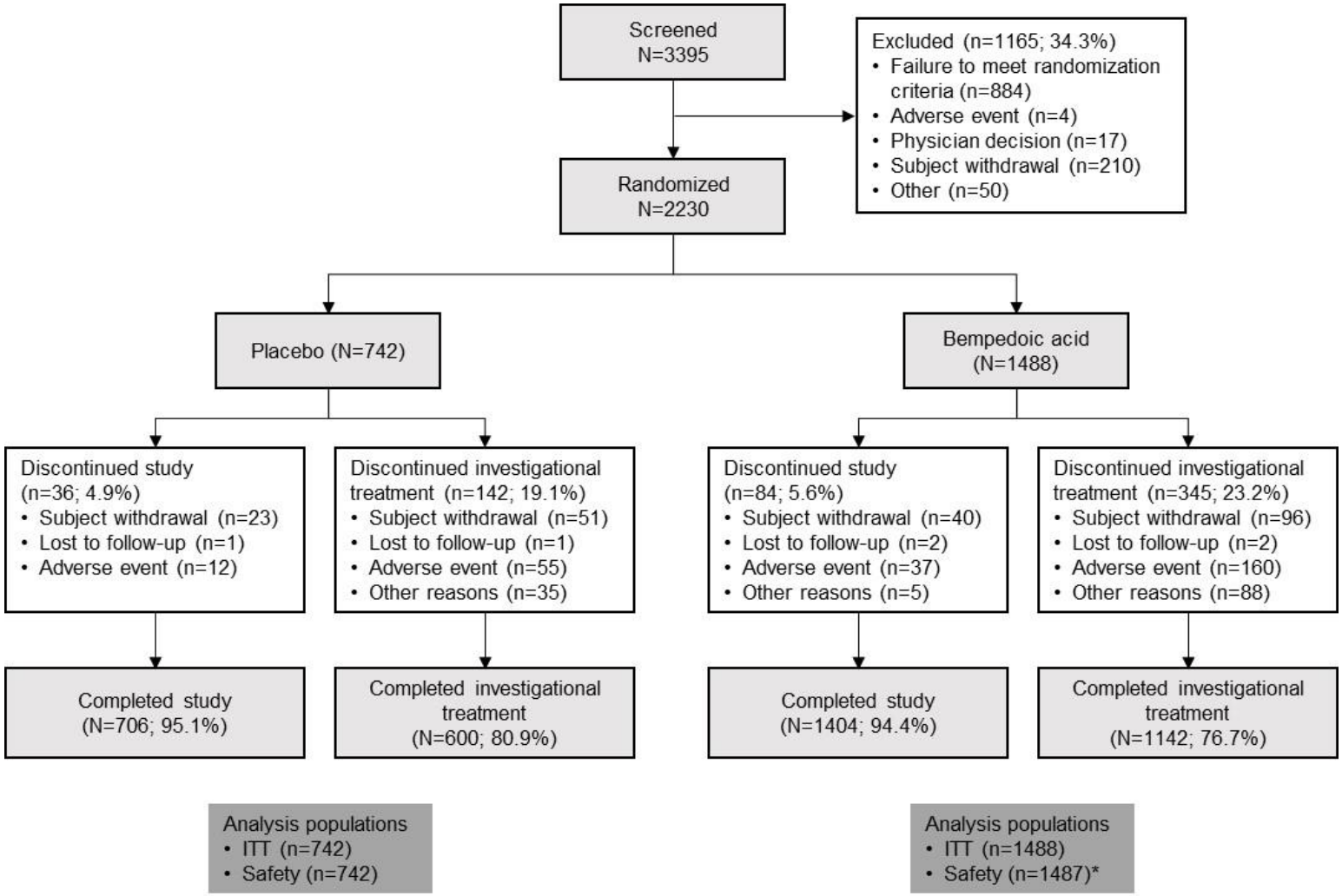
5. Supplementary Figures

5.1 Figure S1. Bempedoic Acid Mechanism of Action

ACSVL1, very long-chain acyl-CoA synthetase 1; BA, bempedoic acid; CoA, coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor.



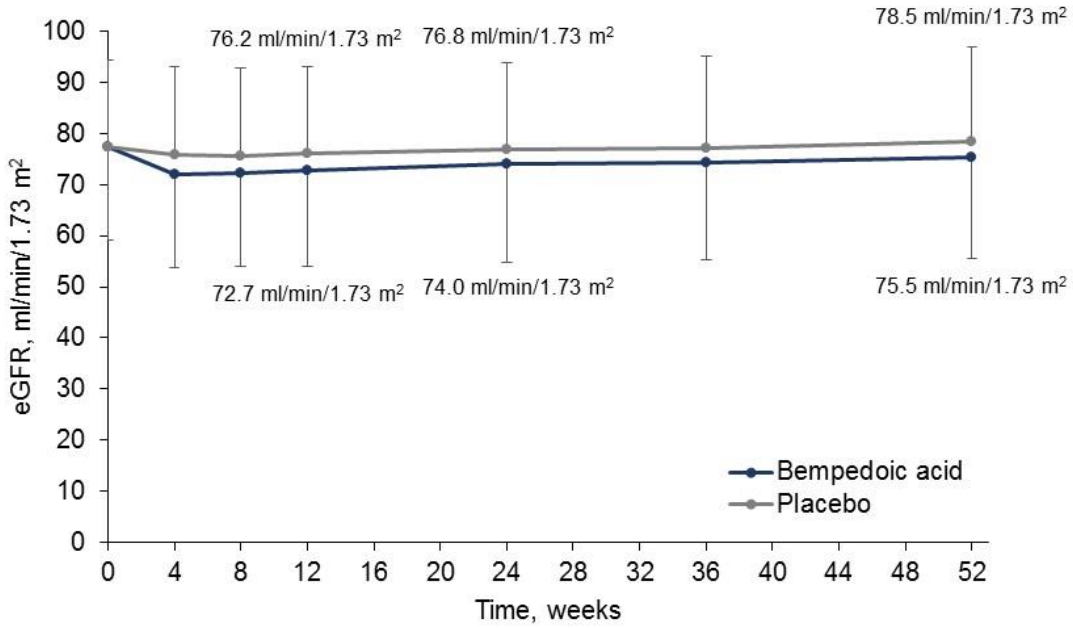
5.2 Figure S2. Patient Disposition



ITT, intention-to-treat
*One patient randomized to bempedoic acid did not receive any dose of study medication and was, therefore, excluded from the safety population..

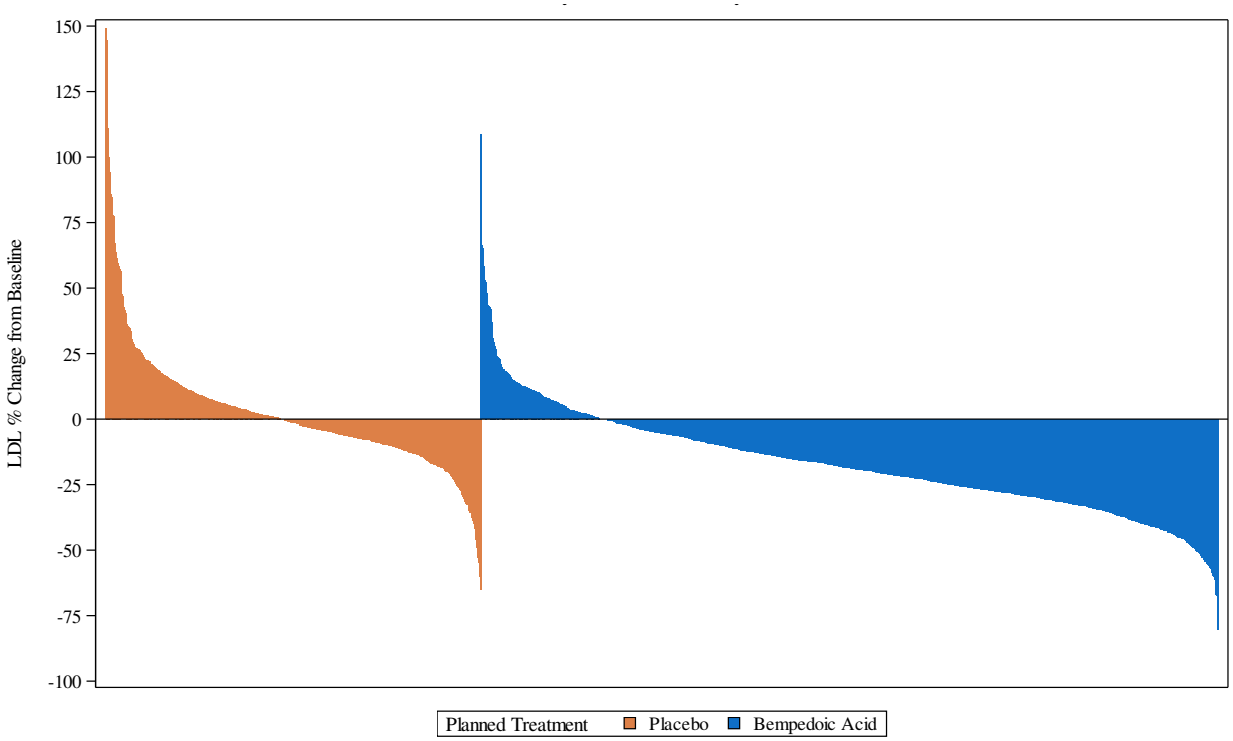
5.3 Figure S3. Estimated Glomerular Filtration Rate (eGFR) (Safety Population).

Data are means ± standard deviations. Baseline eGFR was 77.4 ml/min/1.73m^2 in the placebo treatment group and was stable during the course of the study. Baseline eGFR was 77.5 ml/min/1.73m^2 in the bempedoic acid treatment group, and a slight decline was observed post baseline. Although the differences in eGFR were nominally significant between treatment groups, the magnitude of the differences were not considered to be clinically meaningful.



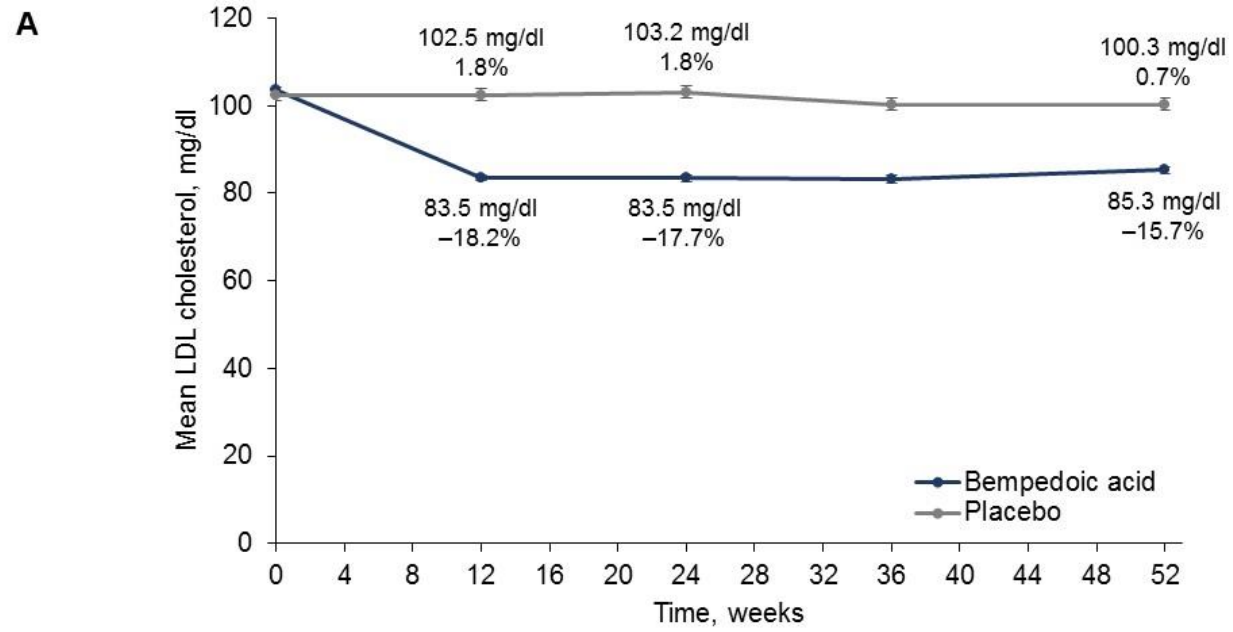
Bempedoic acid, n	1487	1434	1401	1427			1403			1375			1344
Placebo, n	742	728	720	726			709			693			676

5.4 Figure S4. Percent Change from Baseline in LDL-C at Week 12: Patient-Level Analysis (ITT Population).

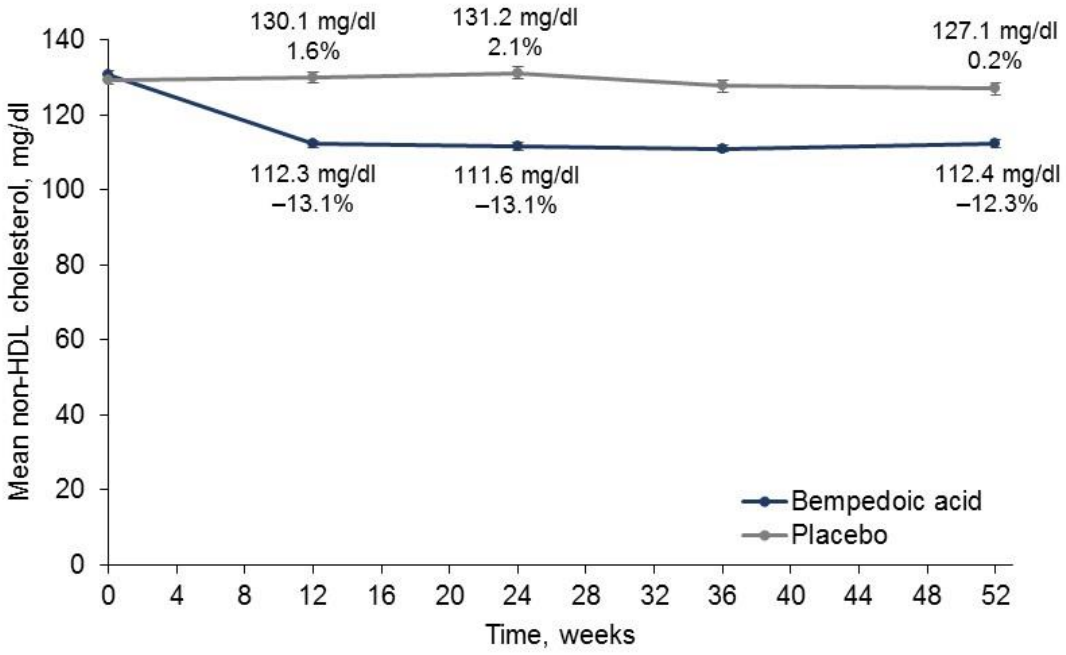


5.5 Figure S5. Efficacy Measures Over the 52-Week Study (Safety Population, On-Treatment Analysis).

Mean or median values for (A) low-density lipoprotein (LDL) cholesterol, (B) non–high-density lipoprotein (HDL) cholesterol, (C) total cholesterol, (D) apolipoprotein B, and (E) high-sensitivity C-reactive protein. For LDL cholesterol, non-HDL cholesterol, and total cholesterol, baseline is defined as the mean of the values at screening and predose on study day 1; for apolipoprotein B and hsCRP baseline is defined as the last value prior to first dose of study drug. Data are means ± standard errors for all parameters except hsCRP, for which median values and 95% confidence intervals are shown.

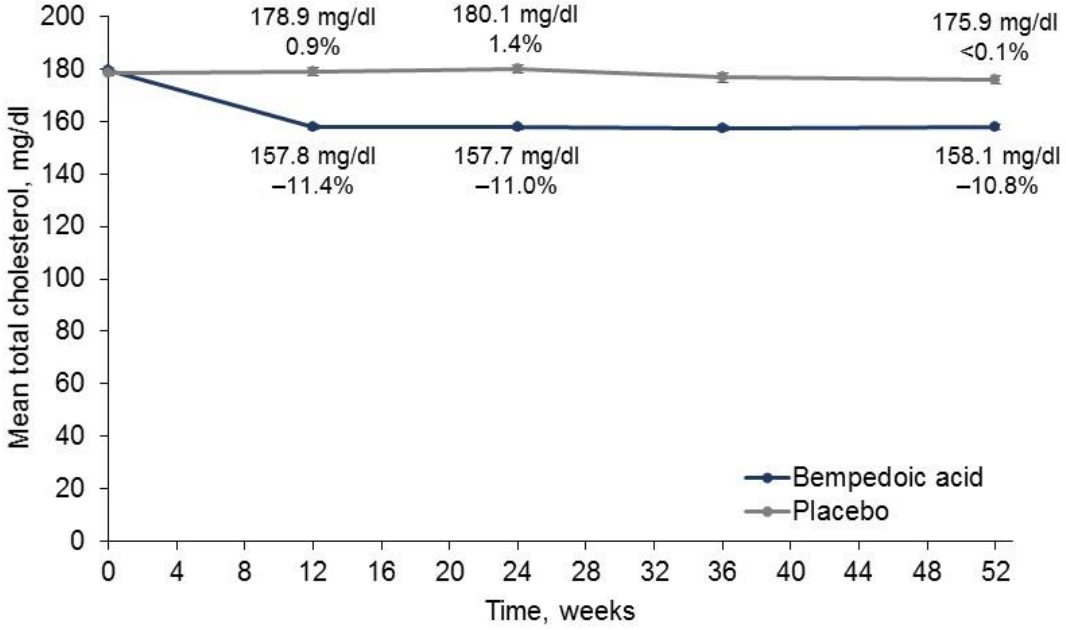


B



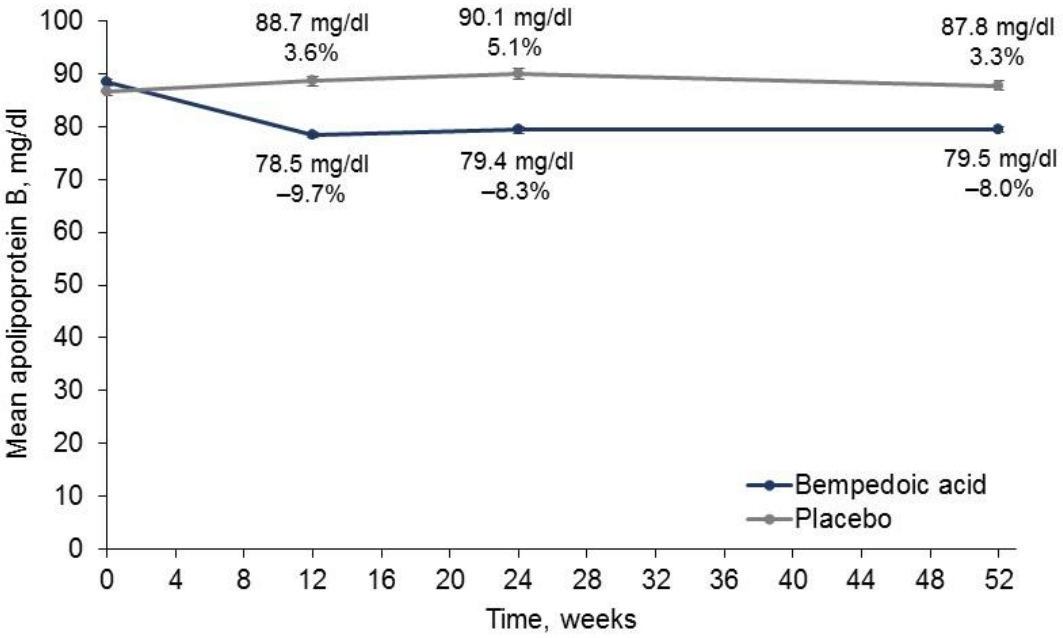
Bempedoic acid, n	1487	1338	1213	1172	1121
Placebo, n	742	696	643	617	589

C



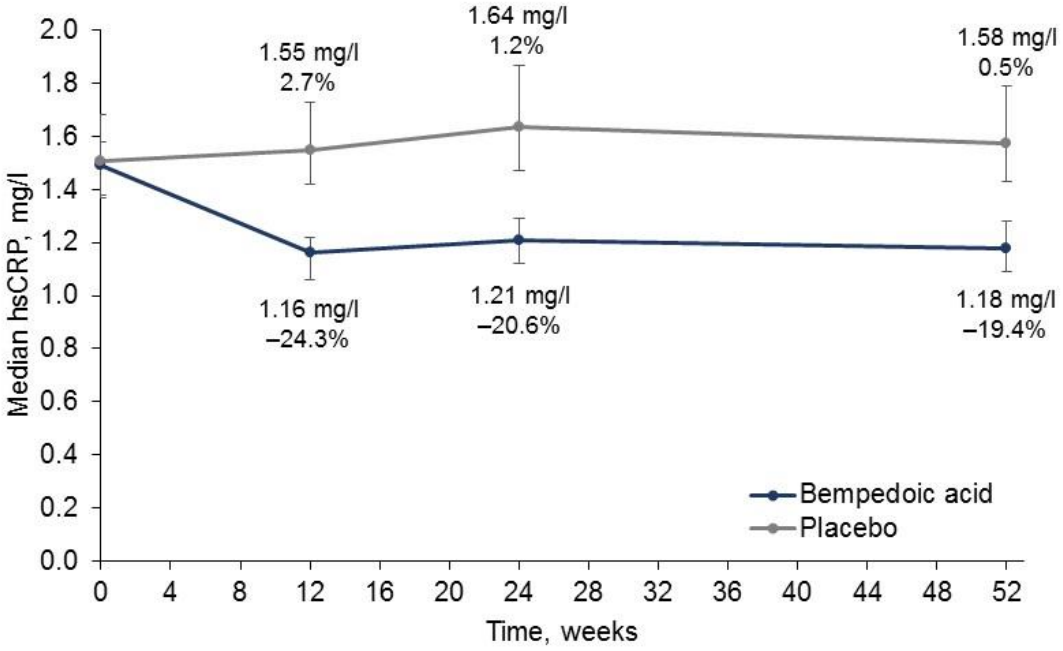
Bempedoic acid, n	1487	1338	1213	1172	1121
Placebo, n	742	696	644	617	589

D



Bempedoic acid, n	1484	1333	1206	1116
Placebo, n	736	688	635	582

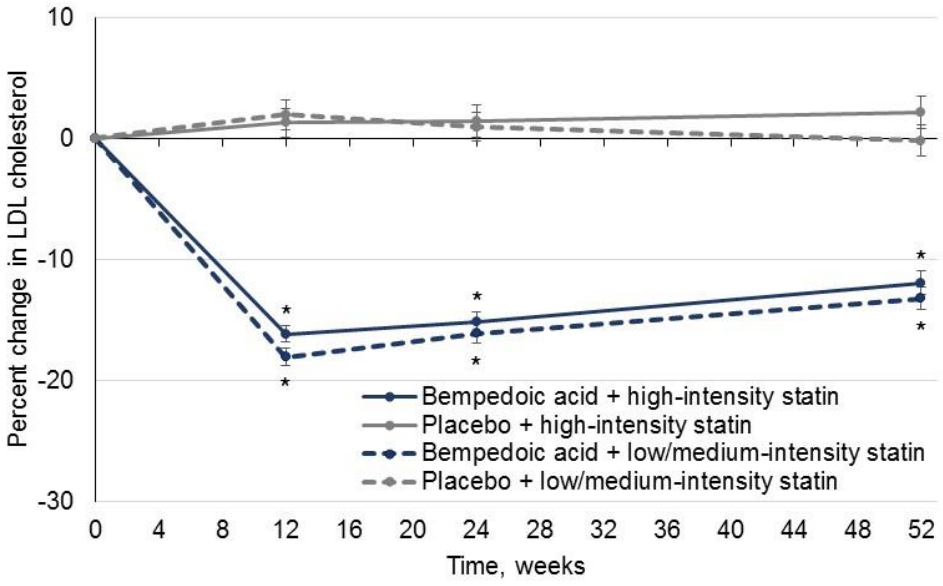
E



Bempedoic acid, n	1486	1334	1212	1119
Placebo, n	739	694	642	586

5.6 Figure S6. Percent Change in LDL-C versus Time by Statin Intensity (ITT Population, On-Treatment Analysis).

Data are least-squares means ± standard errors. Baseline is defined as the mean of the LDL-C values from the last 2 nonmissing values on or prior to study day 1. On-treatment is defined as lab values measured between first dose date and last dose date + 7 days. *P<0.001 for comparison of bempedoic acid and placebo. BA, bempedoic acid.



BA + high-intensity statin, n	752	706	692	678
Placebo + high-intensity statin, n	374	362	356	343
BA +low/med-intensity statin, n	736	718	705	686
Placebo + low/medium-intensity statin, n	368	363	351	342

6. Supplementary Tables

6.1 Table S1. Patient Demographics and Baseline Characteristics (ITT Population).

Characteristics	Placebo (N = 742)	Bempedoic Acid (N = 1488)
Age — yr	66.8 (8.6)	65.8 (9.1)
Male sex — no. (%)	529 (71.3)	1099 (73.9)
White race — no. (%)	716 (96.5)	1423 (95.6)
Region — no. (%)		
North America	259 (34.9)	507 (34.1)
Europe	483 (65.1)	981 (65.9)
Cardiovascular risk factor — no. (%)		
Atherosclerotic cardiovascular disease	727 (98.0)	1449 (97.4)
Heterozygous familial hypercholesterolemia	23 (3.1)	56 (3.8)
Diabetes	212 (28.6)	425 (28.6)
Hypertension	594 (80.1)	1174 (78.9)
Lipid measures at baseline — mg/dl		
Total cholesterol	178.6 (35.6)	179.7 (35.1)
LDL cholesterol	102.3 (30.0)	103.6 (29.1)
Non-HDL cholesterol	129.4 (33.9)	130.9 (33.7)
HDL cholesterol	49.3 (11.5)	48.7 (11.9)
Apolipoprotein B*	86.8 (21.8)	88.5 (21.6)
Triglycerides — mg/dl†	123 (96–170)	126 (98–166)
hsCRP — mg/dl†‡	1.51 (0.79–3.33)	1.49 (0.74–3.28)
Concomitant lipid-modifying therapy		
Statin	742 (100)	1485 (99.8)
Ezetimibe	56 (7.5)	116 (7.8)
Fibrate	26 (3.5)	54 (3.6)
None	0	2 (0.1)
Baseline statin intensity — no. (%)		
Low	48 (6.5)	100 (6.7)
Moderate	324 (43.7)	646 (43.4)
High	370 (49.9)	742 (49.9)
Body mass index — kg/m^2§	29.4 (4.9)	29.7 (4.9)
Renal function category — no. (%)¶		
Normal	167 (22.5)	320 (21.5)
Mild renal impairment	468 (63.1)	946 (63.6)
Moderate renal impairment	107 (14.4)	222 (14.9)
History of tobacco use — no. (%)**		
Current	103 (13.9)	251 (16.9)
Former	405 (54.6)	742 (49.9)
Never	230 (31.0)	484 (32.5)
History of neoplasms benign, malignant, and unspecified (including cysts and polyps) — no. (%)	106 (14.3)	184 (12.4)

HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; ITT, intention to treat; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.
Data are for the ITT population. Values are means (standard deviations) unless otherwise specified. For LDL

cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides, and total cholesterol, baseline is defined as the mean of the values at screening and predose on study day 1; for other parameters, baseline is defined as the last value prior to the first dose of study drug. There were no nominally significant differences between the 2 groups in baseline characteristics with the exception of age (P=0.02), and the difference in age between the 2 groups is not considered clinically important.

*Data were available from 736 patients randomized to placebo and 1485 patients randomized to bempedoic acid.

†Data are medians (interquartile ranges).

‡Data were available from 739 patients randomized to placebo and 1487 patients randomized to bempedoic acid.

§Data were available from 741 patients randomized to placebo and 1486 patients randomized to bempedoic acid.

¶Renal function was categorized by estimated glomerular filtration rate as follows: normal (≥90 ml/min/1.73 m^2), mild renal impairment (60 to 89 ml/min/1.73 m^2), and moderate renal impairment (30 to 59 ml/min/1.73 m^2).

**Data were available from 738 patients randomized to placebo and 1477 patients randomized to bempedoic acid.

6.2 Table S2. Overview of Treatment-emergent Adverse Events and Key Safety Laboratory Findings.*

Variable	Placebo (N = 742)	Bempedoic acid (N = 1487)	Relative Risk (95% CI)†
Adverse events			
Any adverse event	584 (78.7)	1167 (78.5)	1.00 (0.95, 1.04)
Serious adverse event	104 (14.0)	216 (14.5)	1.04 (0.83, 1.29)
Leading to discontinuation of study drug	53 (7.1)	162 (10.9)	1.53 (1.13, 2.05)
Death (all cause)	2 (0.3)	13 (0.9)	3.24 (0.73, 14.34)
Adjudicated MACE	42 (5.7)	68 (4.6)	0.81 (0.56, 1.17)
Cardiovascular death	1 (0.1)	6 (0.4)	2.99 (0.36, 24.82)
Nonfatal myocardial infarction	13 (1.8)	19 (1.3)	0.73 (0.36, 1.47)
Nonfatal stroke	2 (0.3)	5 (0.3)	1.25 (0.24, 6.41)
Coronary revascularization	24 (3.2)	38 (2.6)	0.79 (0.48, 1.31)
Hospitalization for unstable angina	11 (1.5)	14 (0.9)	0.64 (0.29, 1.39)
Other MACE-related events			
Noncoronary arterial revascularization	6 (0.8)	4 (0.3)	0.33 (0.09, 1.18)
Hospitalization for heart failure	1 (0.1)	9 (0.6)	4.49 (0.57, 35.38)
Noncardiovascular death‡	1 (0.1)	2 (0.1)	1.00 (0.09, 10.99)
Non-treatment-emergent death§	0	5 (0.3)	NC
Adverse events of special interest			
Muscular disorders	75 (10.1)	195 (13.1)	1.30 (1.01, 1.67)
Leading to discontinuation of study drug	14 (1.9)	31 (2.1)	1.10 (0.59, 2.06)
Myalgia	45 (6.1)	89 (6.0)	0.99 (0.70, 1.40)
Muscle spasms	20 (2.7)	62 (4.2)	1.55 (0.94, 2.54)
Pain in extremity	16 (2.2)	50 (3.4)	1.56 (0.89, 2.72)
Muscular weakness	4 (0.5)	9 (0.6)	1.12 (0.35, 3.63)
New onset or worsening diabetes	40 (5.4)	49 (3.3)	0.61 (0.41, 0.92)
Gout	2 (0.3)	18 (1.2)	4.49 (1.04, 19.30)
Blood creatinine increased	3 (0.4)	12 (0.8)	2.00 (0.56, 7.05)
Glomerular filtration rate decreased	0	8 (0.5)	NC
Neurocognitive disorders	7 (0.9)	11 (0.7)	0.78 (0.31, 2.01)
Laboratory results			
ALT or AST >3 × ULN‖	1 (0.1)	7 (0.5)	3.49 (0.43, 28.34)
Creatine kinase >5 × ULN‖	1 (0.1)	7 (0.5)	3.49 (0.43, 28.34)
Change from baseline in uric acid – mg/dl¶	–0.06 (0.87)	0.73 (1.11)	NC
Change from baseline in creatinine — mg/dl¶	–0.02 (0.12)	0.02 (0.13)	NC
Creatinine change from baseline of >1 mg/dl	0	2 (0.1)	NC
eGFR <30 mL/min/1.73 m^2	3 (0.4)	14 (0.9)	2.33 (0.67, 8.08)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiac events; NC, not calculated; ULN, upper limit of normal.
Data are number of patients (percentage) unless otherwise specified.
*Includes events occurring from the first dose through 30 days after the last dose of study drug.
†Relative risks and confidence intervals were calculated as a post hoc analysis.
‡Noncardiovascular deaths were due to septic shock secondary to cecal perforation and acute peritonitis for 1 patient in the placebo group, and 1 case each of liver metastases of unknown primary origin and multi-organ failure in the bempedoic acid group.
§Treatment-emergent deaths occurred within 30 days of last study drug dose; deaths deemed not treatment

emergent occurred >30 days after last study drug dose but were related to a fatal adverse event that had an onset within 30 days of last study drug dose. Adverse events resulting in non-treatment-emergent fatality included 1 case of pancreatic pseudocyst and 4 cases of lung cancer.
‖Includes elevations of greater than 3 (aminotransferase) or 5 (creatine kinase) times the ULN that have been repeated and confirmed.
¶Data are mean changes (standard deviations) from baseline to week 52 for 680 (uric acid) and 677 (creatinine) patients in the placebo group and 1358 (uric acid) and 1343 (creatinine) patients in the bempedoic acid group.

6.3 Table S3. Treatment-Emergent Adverse Events (Safety Population).*

Variable	Placebo (N = 742)	Bempedoic acid (N = 1487)
	No. of patients (%)	
Nasopharyngitis	87 (11.7)	146 (9.8)
Myalgia	45 (6.1)	89 (6.0)
Upper respiratory tract infection	31 (4.2)	72 (4.8)
Urinary tract infection	47 (6.3)	71 (4.8)
Arthralgia	44 (5.9)	65 (4.4)
Dizziness	31 (4.2)	65 (4.4)
Muscle spasms	20 (2.7)	62 (4.2)
Diarrhea	30 (4.0)	61 (4.1)
Back pain	18 (2.4)	56 (3.8)
Bronchitis	19 (2.6)	53 (3.6)
Pain in extremity	16 (2.2)	50 (3.4)
Cough	23 (3.1)	47 (3.2)
Headache	24 (3.2)	46 (3.1)
Anemia	16 (2.2)	43 (2.9)
Hypertension	26 (3.5)	43 (2.9)
Nausea	19 (2.6)	43 (2.9)
Lower respiratory tract infection	19 (2.6)	41 (2.8)
Musculoskeletal pain	19 (2.6)	41 (2.8)
Fatigue	25 (3.4)	38 (2.6)
Blood creatinine phosphokinase increased	13 (1.8)	35 (2.4)
Hypoglycemia	22 (3.0)	32 (2.2)
Noncardiac chest pain	17 (2.3)	32 (2.2)
Angina pectoris	25 (3.4)	31 (2.1)
Osteoarthritis	26 (3.5)	30 (2.0)
Constipation	18 (2.4)	27 (1.8)
Sinusitis	18 (2.4)	26 (1.7)
Dyspnea	16 (2.2)	21 (1.4)

*Treatment-emergent adverse events that occurred in ≥2% of patients in either treatment group.

6.4 Table S4. Treatment-emergent Adverse Events by Background Statin Intensity.

	Low-intensity Statin			Moderate-intensity Statin			High-intensity Statin		
	Placebo (n = 47)	**BA (n = 99)**	**RR (95% CI)**	**Placebo (n = 327)**	**BA (n = 652)**	**RR (95% CI)**	**Placebo (n = 368)**	**BA (n = 736)**	**RR (95% CI)**
Adverse events (AEs)									
Any AE	37 (78.7)	80 (80.8)	1.03 (0.86, 1.23)	259 (79.2)	513 (78.7)	0.99 (0.93, 1.06)	288 (78.3)	574 (78.0)	1.00 (0.93, 1.06)
Serious AEs	5 (10.6)	15 (15.2)	1.42 (0.55, 3.69)	46 (14.1)	89 (13.7)	0.97 (0.70, 1.35)	53 (14.4)	112 (15.2)	1.06 (0.78, 1.43)
Muscle-related AE*	8 (17.0)	22 (22.2)	1.31 (0.63, 2.71)	36 (11.0)	84 (12.9)	1.17 (0.81, 1.69)	31 (8.4)	89 (12.1)	1.44 (0.97, 2.12)
Common AEs†									
Nasopharyngitis	5 (10.6)	8 (8.1)	0.76 (0.26, 2.20)	42 (12.8)	59 (9.0)	0.70 (0.49, 1.02)	40 (10.9)	79 (10.7)	0.99 (0.69, 1.41)
Myalgia	6 (12.8)	11 (11.1)	0.87 (0.34, 2.21)	22 (6.7)	43 (6.6)	0.98 (0.60, 1.61)	17 (4.6)	35 (4.8)	1.03 (0.58, 1.81)
Urinary tract infection	4 (8.5)	11 (11.1)	1.31 (0.44, 3.88)	21 (6.4)	27 (4.1)	0.64 (0.37, 1.12)	22 (6.0)	33 (4.5)	0.75 (0.44, 1.27)
Pain in extremity	1 (2.1)	8 (8.1)	3.80 (0.49, 29.49)	8 (2.4)	23 (3.5)	1.44 (0.65, 3.19)	7 (1.9)	19 (2.6)	1.36 (0.58, 3.20)
Dizziness	3 (6.4)	5 (5.1)	0.79 (0.20, 3.17)	16 (4.9)	30 (4.6)	0.94 (0.52, 1.70)	12 (3.3)	30 (4.1)	1.25 (0.65, 2.41)
Arthralgia	1 (2.1)	5 (5.1)	2.37 (0.29, 19.75)	23 (7.0)	25 (3.8)	0.55 (0.31, 0.95)	20 (5.4)	35 (4.8)	0.88 (0.51, 1.49)
URTI	1 (2.1)	2 (2.0)	0.95 (0.09, 10.21)	9 (2.8)	20 (3.1)	1.11 (0.51, 2.42)	21 (5.7)	50 (6.8)	1.19 (0.73, 1.95)
Fatigue	3 (6.4)	5 (5.1)	0.79 (0.20, 3.17)	17 (5.2)	17 (2.6)	0.50 (0.26, 0.97)	5 (1.4)	16 (2.2)	1.60 (0.59, 4.33)

BA, bempedoic acid; RR, relative risk; URTI, upper respiratory tract infection.
Data are number of patients (percentage) unless otherwise specified.
*Muscle-related adverse events were predefined as muscle spasms, myalgia, muscular weakness, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinemia, myoglobinuria, myopathy, myopathy toxic, muscle necrosis, necrotizing myositis, pain in extremity, and rhabdomyolysis.
†Treatment-emergent adverse events reported by at least 6% of patients in any treatment and statin intensity subgroup.

6.5 Table S5. Change From Baseline in Efficacy End Points at Week 12 (ITT Population).

Parameter Treatment Group	N	Mean Change (SD), mg/dl or mg/l	Percent Change LS Mean (SE)	Between Group Difference in Percent Change (95% CI)	P Value
LDL cholesterol, mg/dl					
Bempedoic acid	1488	–19.2 (24.0)	–16.5 (0.52)	–18.1 (–20.0 to –16.1)	<0.001
Placebo	742	0.4 (27.0)	1.6 (0.86)		
Non-HDL cholesterol, mg/dl					
Bempedoic acid	1488	–17.7 (27.7)	–11.9 (0.48)	–13.3 (–15.1 to –11.6)	<0.001
Placebo	742	0.7 (30.0)	1.5 (0.76)		
Total cholesterol, mg/dl					
Bempedoic acid	1488	–20.7 (28.9)	–10.3 (0.37)	–11.1 (–12.5 to –9.8)	<0.001
Placebo	742	0.4 (31.1)	0.8 (0.57)		
Apolipoprotein B, mg/dl					
Bempedoic acid	1485	–9.5 (17.2)	–8.6 (0.47)	–11.9 (–13.6 to –10.2)	<0.001
Placebo	736	1.9 (17.7)	3.3 (0.70)		
hsCRP, mg/l					
Bempedoic acid	1421	–0.22 (1.35)*	–22.4 (72.5)*	–21.5 (–27.0 to –16.0)	<0.001
Placebo	724	0.02 (1.29)*	2.6 (91.9)*		

CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; ITT, intention-to-treat; LDL, low-density lipoprotein; LS, least-squares; SD, standard deviation; SE, standard error.

Percent change from baseline for LDL cholesterol, non-HDL cholesterol, total cholesterol, and apolipoprotein B was analyzed using analysis of covariance, with treatment and randomization strata (heterozygous familial hypercholesterolemia vs. atherosclerotic cardiovascular disease, and high-intensity statin vs. other statin) as factors and baseline lipid parameter as a covariate. For LDL cholesterol, non-HDL cholesterol, and total cholesterol, baseline is defined as the mean of the values at screening and predose on study day 1; for apolipoprotein B and hsCRP, baseline is defined as the last value prior to first dose of study drug. Missing data for LDL cholesterol, non-HDL cholesterol, total cholesterol, and apolipoprotein B were imputed through multiple imputation using a pattern mixture model to account for treatment adherence. Analysis for hsCRP was based on Wilcoxon rank sum test and Hodges-Lehmann estimates for location shift and confidence interval.

*Data are medians (interquartile ranges).

6.6 Table S6. Change From Baseline in Efficacy End Points (Safety Population, On-treatment Analysis).

Parameter Treatment Group	Week 12 Mean Change (SD), mg/dl or mg/l	Week 12 Percent Change Between Group Difference (95% CI)	Week 24 Mean Change (SD), mg/dl or mg/l	Week 24 Percent Change Between Group Difference (95% CI)	Week 52 Mean Change (SD), mg/dl or mg/l	Week 52 Percent Change Between Group Difference (95% CI)
LDL cholesterol, mg/dl						
Bempedoic acid	–20.1 (23.3)	–19.8	–19.6 (24.4)	–19.4	–17.7 (26.7)	–16.1
Placebo	0.4 (27.1)	(–21.7 to –17.8)	0.9 (25.1)	(–21.5 to –17.3);	–0.6 (24.0)	(–18.3 to –13.8)
Non-HDL cholesterol, mg/dl						
Bempedoic acid	–18.5 (27.2)	–14.5	–18.5 (28.0)	–15.1	–17.7 (30.1)	–12.2
Placebo	0.6 (30.2)	(–16.3 to –12.8)	1.7 (28.4)	(–17.0 to –13.2)	1.0 (27.3)	(–14.2 to –10.3)
Total cholesterol, mg/dl						
Bempedoic acid	–21.7 (28.3)	–12.2	–21.1 (29.5)	–12.4	–20.8 (31.2)	–10.6
Placebo	0.3 (31.1)	(–13.5 to –10.8)	1.7 (28.9)	(–13.8 to –11.0)	–1.1 (28.0)	(–12.0 to –9.1)
Apolipoprotein B, mg/dl						
Bempedoic acid	–10.0 (16.9)	–12.9	–8.7 (17.8)	–13.0	–8.5 (19.2)	–10.8
Placebo	1.8 (17.7)	(–14.5 to –11.2)	3.2 (17.3)	(–14.8 to –11.1)	1.6 (17.0)	(–12.7 to –8.9)
hsCRP, mg/l						
Bempedoic acid	–0.24 (1.37)*	–22.6	–0.20 (1.44)*	–20.8	–0.17 (1.42)*	–18.6
Placebo	0.02 (1.29)*	(–28.2 to –17.0)	0.02 (1.30)*	(–26.8 to –14.8)	0.01 (1.34)*	(–25.3 to –12.0)

CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SD, standard deviation.
Percent change from baseline for LDL cholesterol, non-HDL cholesterol, total cholesterol, and apolipoprotein B was analyzed using analysis of covariance, with treatment and randomization strata (heterozygous familial hypercholesterolemia vs. atherosclerotic cardiovascular disease, and high-intensity statin vs. other statin) as factors and baseline lipid parameter as a covariate. For LDL cholesterol, non-HDL cholesterol, and total cholesterol, baseline is defined as the mean of the values at screening and predose on study day 1; for apolipoprotein B and hsCRP, baseline is defined as the last value prior to first dose of study drug. On-treatment analysis used data collected during the treatment period only (i.e., up to the date of last dose + 7); any data collected after 7 days post last dose of study drug were excluded. Analysis for hsCRP was based on Wilcoxon rank sum test and Hodges-Lehmann estimates for location shift and confidence interval.
*Data are medians (interquartile ranges).

6.7 Table S7. Change from Baseline for Additional Safety and Lipid Parameters (ITT Population).

		Placebo			Bempedoic Acid	
Parameter	**N**	**Mean Change, mg/dl or kg**	**Percent Change**	**N**	**Mean Change, mg/dl or kg**	**Percent Change**
HDL cholesterol, mg/dl						
Change at week 12	726	–0.27 (5.52)	–0.09 (11.2)	1427	–2.98 (6.77)	–5.92 (13.5)
Change at week 24	707	0.18 (6.17)	0.94 (12.3)	1396	–2.29 (7.36)	–4.43 (14.9)
Change at week 36	692	0.23 (6.20)	1.11 (12.8)	1375	–2.07 (7.18)	–4.04 (14.6)
Change at week 52	685	–0.12 (6.22)	0.36 (12.8)	1364	–2.64 (7.04)	–5.25 (14.3)
Triglycerides, mg/dl						
Change at week 12	726	–0.50 (–21.5, 23.5)*	–0.33 (–16.9, 20.8)*	1427	3.00 (–19.5, 32.0)*	2.90 (–15.8, 26.2)*
Change at week 24	707	1.00 (–20.0, 23.5)*	0.81 (–14.9, 20.4)*	1396	2.50 (–22.3, 30.5)*	2.24 (–17.1, 25.3)*
Change at week 36	692	–1.50 (–20.8, 24.0)*	–1.16 (–16.0, 20.9)*	1375	–0.50 (–25.0, 30.0)*	–0.43 (–19.3, 24.0)*
Change at week 52	685	–3.00 (–25.5, 18.0)*	–3.17 (–18.3, 16.1)*	1364	–5.00 (–27.5, 23.0)*	–4.54 (–21.8, 18.8)*
Weight, kg						
Change at week 4	729	–0.04 (3.56)	NC	1439	–0.10 (2.13)	NC
Change at week 8	720	–0.07 (3.34)		1404	–0.09 (3.11)	
Change at week 12	726	0.11 (3.44)		1430	–0.26 (2.75)	
Change at week 24	711	0.02 (3.91)		1406	–0.38 (3.18)	
Change at week 36	694	–0.14 (4.09)		1375	–0.55 (4.19)	
Change at week 52	687	–0.22 (4.43)		1370	–0.79 (4.16)	

HDL, high-density lipoprotein; ITT, intention-to-treat; NC, not calculated.
Baseline is defined as the mean of the values at screening and predose on study day 1.
Data are means (standard deviations) unless otherwise noted.
*Data are medians (Q1, Q3).

6.8 Table S8. Percent of Patients Achieving LDL Cholesterol <70 mg/dl at Week 12 (ITT Population).

	Patients, n/N (%)		
	Placebo	**Bempedoic Acid**	**P Value**
Week 12	65/725 (9.0)	461/1424 (32.4)	<0.001
Week 24	72/707 (10.2)	447/1397 (32.0)	<0.001
Week 52	65/685 (9.5)	384/1364 (28.2)	<0.001

LDL, low-density lipoprotein; ITT, intention-to-treat.
N' is the number of patients per treatment group with nonmissing values at a given timepoint.

7. References

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