Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less than Low Dose Statins

Summary

EudraCT number	2016-004084-39
Trial protocol	HU GB DE CZ
Global end of trial date	11 January 2018

Results information

Result version number	v1 (current)
This version publication date	20 March 2019
First version publication date	20 March 2019

Trial information

Trial identification

Sponsor protocol code	1002-048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03001076
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Esperion Therapeutics Inc.
Sponsor organisation address	Bldg. I: 3891 Ranchero Drive, Suite 150, Ann Arbor, Michigan, United States, 48108
Public contact	Director of Clinical Operations, Esperion Therapeutics, 00 1 7348873903, clinicaltrials@esperion.com
Scientific contact	Director of Clinical Operations, Esperion Therapeutics, 00 1 7348873903, clinicaltrials@esperion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing low-density lipoprotein cholesterol (LDL-C) when added to ezetimibe therapy in participants with elevated LDL-C.

Protection of trial subjects:

The trial was designed, conducted, and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy:

All participants received study supplied ezetimibe 10 mg/day as background therapy throughout the study. Participants on low or very low-dose statin at screening could continue statin therapy throughout the study provided that the dose was stable (≥4 weeks) and well tolerated. Low dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. Very low-dose statin therapy was defined as an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg. Participants were instructed to continue taking their lipid-modifying therapy (LMT) throughout the study. PCSK9 inhibitors were not allowed during the study period. Other LMTs were to remain stable for at least 4 weeks prior to screening; fibrates (with the exception of gemfibrozil which was exclusionary in participants aking a statin) were to remain stable for at least 6 weeks prior to screening.

Evidence for comparator: -

Actual start date of recruitment	29 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 203
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 7
Worldwide total number of subjects	269
EEA total number of subjects	49

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	122
From 65 to 84 years	143
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Out of the 269 participants who were randomized to the double-blind treatment period, 181 participants were randomized to bempedoic acid and 88 participants to placebo. One participant in the placebo group was randomized but never started treatment.

Pre-assignment

Screening details:

The study consisted of an approximate 1-week screening period, a 4-week single-blind placebo and ezetimibe run-in period, and a 12-week double-blind treatment period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The Sponsor, all clinical site personnel (investigator, pharmacist, etc.), and other vendor personnel were blinded to the treatment group for each participant. Participants were also blinded to the treatment they received. Bempedoic acid and placebo had identical physical appearance and packaging. Blinding of treatment was maintained for all participants unless, in the opinion of the investigator, the safety of the participant was at risk.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 4 weeks prior to the 12-week treatment period. During the treatment period, participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received ezetimibe 10 mg capsule, once-daily by mouth for 4 weeks during the run-in period and 12 weeks during the treatment period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo tablet, once-daily by mouth for 4 weeks during the run-in period and 12 weeks during the treatment period.

Arm title	Bempedoic Acid

Arm description:

Participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 4 weeks prior to the 12-week treatment period. During the treatment period, participants received bempedoic acid 180 mg tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily

by mouth for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo tablet, once-daily by mouth, with or without food for 4 weeks during the run-in period.

Investigational medicinal product name	Bempedoic acid
Investigational medicinal product code	ETC-1002
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received bempedoic acid 180 mg tablet, once-daily by mouth, with or without food for 12 weeks during the treatment period.

Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received ezetimibe 10 mg capsule, once-daily by mouth for 4 weeks during the run-in period and 12 weeks during the treatment period.

Number of subjects in period 1	Placebo	Bempedoic Acid
Started	88	181
Completed	81	176
Not completed	7	5
Adverse event, non-fatal	3	3
Unknown	1	-
Sponsor decision	1	-
Lost to follow-up	-	2
Withdrawal by patient	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 4 weeks prior to the 12-week treatment period. During the treatment period, participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 12 weeks.	
Reporting group title	Bempedoic Acid
Reporting group description:	
Participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 4 weeks prior to the 12-week treatment period. During the treatment period, participants received bempedoic acid 180 mg tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 12 weeks.	

Reporting group values	Placebo	Bempedoic Acid	Total
Number of subjects	88	181	269
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.7	63.8	
standard deviation	± 11.32	± 10.77	-
Gender categorical Units: Subjects			
Female	56	109	165
Male	32	72	104
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	3	4
Native Hawaiian or Other Pacific Islander	0	2	2
Black or African American	10	11	21
White	75	165	240
More than one race	2	0	2
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	23	43	66
Not Hispanic or Latino	65	138	203
Unknown or Not Reported	0	0	0
LDL-C category Units: Subjects			
<130 mg/dL	56	99	155
≥130 to <160 mg/dL	24	53	77
≥160 mg/dL	8	29	37
Concomitant lipid-modifying therapy medications			

Concomitant medications were defined as medications that started prior to, on or after the first dose of double-blind IMP and started no later than 30 days following end of double-blind IMP, and ended on or after the date of first dose of double-blind IMP or were ongoing at the end of the study. Other LMT included fish oil, eicosapentaenoic acid ethyl ester, omega-3 fatty acids, salmon oil, and sitosterol. Participants received ezetimibe 10 mg/day as background therapy throughout the study. Participants who took at least one concomitant LMT have been reported.			
Units: Subjects			
Statins	25	59	84
Fibrates	3	7	10
Nicotinic acid and derivatives	4	3	7
Bile acid sequestrants	1	1	2
Other lipid-modifying therapies	8	19	27
No concomitant lipid-modifying therapies	47	92	139
Concomitant illness: Cardiac disorder			
Concomitant illness was defined as the present condition that started prior to the date of randomization and was ongoing at the time of randomization.			
Units: Subjects			
Participants with cardiac disorder	22	49	71
Participants without cardiac disorder	66	132	198
History of diabetes Units: Subjects			
Participants with history of diabetes	17	35	52
Participants without history of diabetes	71	146	217
History of hypertension Units: Subjects			
Participants with history of hypertension	51	111	162
Participants without history of hypertension	37	70	107
Estimated glomerular filtration rate (eGFR) category			
milliliter per minutes per 1.73 square meter (mL/min/1.73m2)			
Units: Subjects			
≥90 mL/min/1.73m2	17	45	62
60 to <90 mL/min/1.73m2	57	110	167
<60 mL/min/1.73m2	14	26	40
Low-density lipoprotein cholesterol (LDL-C)			
Baseline was defined as the mean of the last two non-missing values on or prior to Day 1.			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean	123.02	129.77	
standard deviation	± 27.197	± 30.871	-
Non-high-density lipoprotein cholesterol (non-HDL-C)			
Baseline was defined as the mean of the last two non-missing values on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	151.55	162.41	
standard deviation	± 32.734	± 35.413	-
Total cholesterol (TC)			
Baseline was defined as the mean of the last two non-missing values on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	208.62	218.24	
standard deviation	± 35.712	± 35.883	-

Apolipoprotein B (apoB)			
Baseline was defined as the last non-missing value on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	115.8	123.3	
standard deviation	± 23.47	± 26.48	-
High-sensitivity C-reactive protein (hsCRP)			
Baseline was defined as the last non-missing value on or prior to Day 1.			
Units: mg/dL			
median	2.260	2.205	
full range (min-max)	0.13 to 14.37	0.22 to 39.20	-
Triglycerides (TGs)			
Baseline was defined as the mean of the last two non-missing values on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	143.39	166.93	
standard deviation	± 61.932	± 75.683	-
High-density lipoprotein cholesterol (HDL-C)			
Baseline was defined as the mean of the last two non-missing values on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	57.07	55.84	
standard deviation	± 21.319	± 16.326	-
Systolic blood pressure			
Units: millimeter of mercury (mmHg)			
arithmetic mean	126.0	127.3	
standard deviation	± 13.50	± 13.34	-
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	77.0	76.4	
standard deviation	± 7.56	± 8.46	-
Body mass index (BMI)			
Units: kilograms per square meter (kg/m2)			
arithmetic mean	30.45	29.52	
standard deviation	± 5.787	± 4.740	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 4 weeks prior to the 12-week treatment period. During the treatment period, participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 12 weeks.

Reporting group title	Bempedoic Acid

Reporting group description:

Participants received placebo tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 4 weeks prior to the 12-week treatment period. During the treatment period, participants received bempedoic acid 180 mg tablet, once-daily by mouth and ezetimibe 10 mg capsules, once-daily by mouth for 12 weeks.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS), also known as the intention-to-treat set was defined as all randomized participants. Participants in the FAS were included in their randomized treatment group, regardless of their actual treatment.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set (SAS) was defined as all randomized participants who received at least 1 dose of study medication.

Primary: Percent Change From Baseline to Week 12 in Low-Density Lipoprotein Cholesterol (LDL-C)

End point title	Percent Change From Baseline to Week 12 in Low-Density Lipoprotein Cholesterol (LDL-C)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for LDL-C. Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: ([LDL-C value at Week 12 minus Baseline value] divided by [Baseline Value]) multiplied by 100. Bempedoic Acid = BA.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[1]	181[2]		
Units: percent change				
least squares mean (standard error)				
Week 12 (n= 82, 175)	4.99 (± 2.299)	-23.46 (± 1.945)		

Notes:

[1] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. Least square (LS) mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. The missing parameter at Week 12 was imputed using a multiple imputation method taking into account adherence to treatment.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-28.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.376
upper limit	-22.531
Variability estimate	Standard error of the mean
Dispersion value	3.022

Secondary: Percent Change From Baseline to Week 12 in Non-high-density Lipoprotein Cholesterol (non-HDL-C)

End point title	Percent Change From Baseline to Week 12 in Non-high-density Lipoprotein Cholesterol (non-HDL-C)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for non-HDL-C. Baseline was defined as the mean of the non-HDL-C values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: ([non-HDL-C value at Week 12 minus Baseline value] divided by [Baseline Value]) multiplied by 100.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[3]	181[4]		
Units: percent change				
least squares mean (standard error)				
Week 12 (n= 82, 175)	5.19 (± 2.202)	-18.38 (± 1.668)		

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. The missing parameter at Week 12 was imputed using a multiple imputation method taking into account adherence to treatment.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-23.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.005
upper limit	-18.121
Variability estimate	Standard error of the mean
Dispersion value	2.777

Secondary: Percent Change From Baseline to Week 12 in Total Cholesterol (TC)

End point title	Percent Change From Baseline to Week 12 in Total Cholesterol (TC)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for TC. Baseline was defined as the mean of the TC values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: ([TC value at Week 12 minus Baseline value] divided by [Baseline Value]) multiplied by 100.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[5]	181[6]		
Units: Percent change				
least squares mean (standard error)				
Week 12 (n= 82, 176)	2.88 (± 1.553)	-15.11 (± 1.282)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. The missing parameter at Week 12 was imputed using a multiple imputation method taking into account adherence to treatment.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-17.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.94
upper limit	-14.03
Variability estimate	Standard error of the mean
Dispersion value	2.018

Secondary: Percent Change From Baseline to Week 12 in Apolipoprotein B (apoB)

End point title	Percent Change From Baseline to Week 12 in Apolipoprotein B (apoB)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for apoB. Baseline was defined as the last non-missing value on or prior to Day 1. Percent change from baseline was calculated as: [(apoB value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[7]	181[8]		
Units: Percent change				
least squares mean (standard error)				
Week 12 (n= 81, 174)	4.74 (± 1.786)	-14.58 (± 1.497)		

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. The missing parameter at Week 12 was imputed using a multiple imputation method taking into account adherence to treatment.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-19.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.908
upper limit	-14.732
Variability estimate	Standard error of the mean
Dispersion value	2.341

Secondary: Percent Change From Baseline to Week 12 in High-sensitivity C-reactive protein (hsCRP)

End point title	Percent Change From Baseline to Week 12 in High-sensitivity C-reactive protein (hsCRP)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for hsCRP. Baseline was defined as the last non-missing value on or prior to Day 1. Percent change from baseline was calculated as: [(hsCRP value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[9]	181[10]		
Units: Percent change				
median (inter-quartile range (Q1-Q3))				
Week 12 (n= 81, 175)	2.088 (-99999 to 81.367)	-32.521 (-99999 to 66.270)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Location shift

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. The location shift and 95% CI was based on Hodges-Lehman estimation. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon Two Sample Test
Parameter estimate	Location shift
Point estimate	-31.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.761
upper limit	-17.401

Secondary: Percent Change From Baseline to Week 12 in Triglycerides (TGs)

End point title	Percent Change From Baseline to Week 12 in Triglycerides (TGs)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for TGs. Baseline was defined as the mean of the TGs values from the last two non-missing values on or prior to D 1. Percent change from baseline was calculated as: [(TGs value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[11]	181[12]		
Units: Percent change				
least squares mean (standard error)				
Week 12 (n= 82, 176)	9.23 (± 4.218)	4.70 (± 3.068)		

Notes:

[11] - FAS

[12] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-4.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.877
upper limit	5.812
Variability estimate	Standard error of the mean
Dispersion value	5.24

Secondary: Percent Change From Baseline to Week 12 in High-density lipoprotein cholesterol (HDL-C)

End point title	Percent Change From Baseline to Week 12 in High-density lipoprotein cholesterol (HDL-C)

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for HDL-C. Baseline was defined as the mean of the HDL-C values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: [(HDL-C value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[13]	181[14]		
Units: percent change				
least squares mean (standard error)				
Week 12 (n= 82, 175)	-1.38 (± 1.389)	-7.27 (± 1.214)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-5.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.528
upper limit	-2.25
Variability estimate	Standard error of the mean
Dispersion value	1.845

Secondary: Percentage of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Participants With Treatment-emergent Adverse Events (TEAEs)

End point description:

TEAEs, defined as an adverse events (AEs) that began or worsened in severity after the first dose of double-blind study drug and prior to the last dose of double-blind study drug + 30 days, were collected and reported.

End point type	Secondary

End point timeframe:

Up to approximately 16 weeks

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[15]	181[16]		
Units: percentage of participants				
number (not applicable)				
TEAEs	44.8	48.6		
Non-serious TEAEs	20.7	25.4		
Serious TEAEs	3.4	2.8		
Deaths	0	0		

Notes:

[15] - SAS

[16] - SAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Weeks 4 and 8 in LDL-C

End point title	Percent Change From Baseline to Weeks 4 and 8 in LDL-C

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for LDL-C. Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: [(LDL-C value at Week 4 or 8 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Other pre-specified

End point timeframe:

Week 4 and Week 8

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[17]	181[18]		
Units: Percent change				
least squares mean (standard error)				
Week 4 (n= 85, 180)	3.05 (± 1.442)	-28.04 (± 1.704)		
Week 8 (n= 82, 173)	3.61 (± 1.773)	-25.51 (± 1.773)		

Notes:

[17] - FAS

[18] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 4

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-31.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.498
upper limit	-26.682
Variability estimate	Standard error of the mean
Dispersion value	2.238

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 8

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-29.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.074
upper limit	-24.168
Variability estimate	Standard error of the mean
Dispersion value	2.513

Other pre-specified: Percent Change From Baseline to Weeks 4 and 8 in Non-HDL-C

End point title	Percent Change From Baseline to Weeks 4 and 8 in Non-HDL-C

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for Non-HDL-C. Baseline was defined as the mean of the Non-HDL-C values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: [(Non-HDL-C value at Week 4 or 8 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Other pre-specified

End point timeframe:

Week 4 and Week 8

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[19]	181[20]		
Units: Percent change				
least squares mean (standard error)				
Week 4 (n= 85, 180)	3.08 (± 1.362)	-22.17 (± 1.457)		
Week 8 (n= 82, 173)	3.71 (± 1.660)	-20.04 (± 1.531)		

Notes:

[19] - FAS

[20] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 4

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-25.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.204
upper limit	-21.308
Variability estimate	Standard error of the mean
Dispersion value	2.004

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 8

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-23.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.219
upper limit	-19.276
Variability estimate	Standard error of the mean
Dispersion value	2.268

Other pre-specified: Percent Change From Baseline to Weeks 4 and 8 in TC	
End point title	Percent Change From Baseline to Weeks 4 and 8 in TC
End point description:	
Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for TC. Baseline was defined as the mean of the TC values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: [(TC value at Week 4 or 8 minus Baseline value) divided by (Baseline Value)] multiplied by 100.	
End point type	Other pre-specified
End point timeframe:	
Week 4 and Week 8	

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[21]	181[22]		
Units: Percent change				
least squares mean (standard error)				
Week 4 (n= 85, 180)	2.08 (± 1.000)	-18.33 (± 1.129)		
Week 8 (n= 82, 173)	1.82 (± 1.110)	-16.63 (± 1.215)		

Notes:

[21] - FAS

[22] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 4
Statistical analysis description:	
The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed	
Comparison groups	Placebo v Bempedoic Acid

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-20.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.39
upper limit	-17.43
Variability estimate	Standard error of the mean
Dispersion value	1.513

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 8

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-18.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.71
upper limit	-15.206
Variability estimate	Standard error of the mean
Dispersion value	1.651

Other pre-specified: Percent Change From Baseline to Weeks 4 and 8 in TGs

End point title	Percent Change From Baseline to Weeks 4 and 8 in TGs

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for TGs. Baseline was defined as the mean of the TGs values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: [(TGs value at Week 4 or 8 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Other pre-specified

End point timeframe:

Week 4 and Week 8

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[23]	181[24]		
Units: Percent change				
least squares mean (standard error)				
Week 4 (n= 85, 180)	6.00 (± 4.273)	5.20 (± 2.536)		
Week 8 (n= 82, 173)	7.68 (± 4.246)	7.60 (± 2.849)		

Notes:

[23] - FAS

[24] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 4

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.873
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.663
upper limit	9.059
Variability estimate	Standard error of the mean
Dispersion value	4.99

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 8

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.988
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.215
upper limit	10.055
Variability estimate	Standard error of the mean
Dispersion value	5.131

Other pre-specified: Percent Change From Baseline to Weeks 4 and 8 in HDL-C

End point title	Percent Change From Baseline to Weeks 4 and 8 in HDL-C

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for HDL-C. Baseline was defined as the mean of the HDL-C values from the last two non-missing values on or prior to Day 1. Percent change from baseline was calculated as: [(HDL-C value at Week 4 or 8 minus Baseline value) divided by (Baseline Value)] multiplied by 100.

End point type	Other pre-specified

End point timeframe:

Week 4 and Week 8

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[25]	181[26]		
Units: Percent change				
least squares mean (standard error)				
Week 4 (n= 85, 180)	0.85 (± 1.204)	-7.73 (± 1.081)		
Week 8 (n= 82, 173)	-1.33 (± 1.272)	-7.75 (± 1.144)		

Notes:

[25] - FAS

[26] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 4

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-8.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.778
upper limit	-5.394
Variability estimate	Standard error of the mean
Dispersion value	1.619

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 8

Statistical analysis description:

The analysis compared the percent change from baseline between treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval of 95%. LS mean, 95% CI, and P-value was based on an ANCOVA model with percent change from baseline as the dependent variable, treatment as a fixed effects and baseline as a covariate. Observed data was used for the analysis, no imputation for the missing data was performed.

Comparison groups	Placebo v Bempedoic Acid
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-6.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.798
upper limit	-3.049
Variability estimate	Standard error of the mean
Dispersion value	1.712

Other pre-specified: Absolute Change From Baseline to Weeks 4, 8, and 12 in LDL-C

End point title	Absolute Change From Baseline to Weeks 4, 8, and 12 in LDL-C

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analysed for LDL-C. Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Absolute change from baseline was calculated as: LDL-C value at Week 4, 8, or 12 minus Baseline value.

End point type	Other pre-specified

End point timeframe:

Week 4, Week 8 and Week 12

End point values	Placebo	Bempedoic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[27]	181[28]		
Units: milligrams per deciliter (mg/dL)				
geometric mean (standard deviation)				
Change from Baseline at Week 4 (n= 85, 180)	3.6 (± 15.65)	-37.4 (± 30.90)		
Change from Baseline at Week 8 (n= 82, 173)	3.9 (± 19.22)	-34.5 (± 32.29)		
Change from Baseline at Week 12 (n= 82, 175)	5.3 (± 23.96)	-32.9 (± 34.14)		

Notes:

[27] - FAS

[28] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 16 weeks

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), defined as an adverse events (AEs) that began or worsened in severity after the first dose of double-blind study drug and prior to the last dose of double-blind study drug + 30 days, were collected and reported. The analysis was performed using the Safety Analysis Set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Bempedoic Acid

Reporting group description:

Participants received bempedoic acid 180 mg tablet, once-daily by mouth and ezetimibe 10 mg capsule, once-daily by mouth for 12 weeks during the treatment period.

Serious adverse events	Placebo	Bempedoic Acid	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 87 (3.45%)	5 / 181 (2.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Poisoning deliberate			

subjects affected / exposed	1 / 87 (1.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 87 (1.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 87 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 87 (1.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Bempedoic Acid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 87 (20.69%)	46 / 181 (25.41%)	
Investigations			
Blood uric acid increase			
subjects affected / exposed	2 / 87 (2.30%)	14 / 181 (7.73%)	
occurrences (all)	2	14	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 87 (0.00%)	4 / 181 (2.21%)	
occurrences (all)	0	4	
Liver function test increased			
subjects affected / exposed	0 / 87 (0.00%)	7 / 181 (3.87%)	
occurrences (all)	0	7	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 87 (3.45%)	8 / 181 (4.42%)	
occurrences (all)	3	8	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 87 (2.30%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 87 (0.00%)	5 / 181 (2.76%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			

Muscle spasms			
subjects affected / exposed	3 / 87 (3.45%)	6 / 181 (3.31%)	
occurrences (all)	4	6	
Myalgia			
subjects affected / exposed	2 / 87 (2.30%)	3 / 181 (1.66%)	
occurrences (all)	4	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 87 (1.15%)	4 / 181 (2.21%)	
occurrences (all)	1	4	
Sinusitis			
subjects affected / exposed	0 / 87 (0.00%)	5 / 181 (2.76%)	
occurrences (all)	0	5	
Urinary tract infection			
subjects affected / exposed	5 / 87 (5.75%)	5 / 181 (2.76%)	
occurrences (all)	5	7	
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 87 (2.30%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 87 (2.30%)	2 / 181 (1.10%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2017	Protocol Amendment 2, dated 10 February 2017, included the following key changes: • Changed protocol title to more accurately reflect the study population based on guidance from the Food and Drug Administration (FDA) • Updated the bempedoic acid mechanism of action • Revised various inclusion criterion and exclusion criterion • Excluded use of cholesteryl ester transfer protein inhibitor (CETP) inhibitors • Changed exclusion time period for mipomersen to 6 months • Removed the allowance to rescreen if low-density lipoprotein cholesterol (LDL-C) criteria at screening visit 1 (S1) were not met • Extended screening an additional 4 weeks if needed to adjust background therapy • Removed collection of pharmacokinetic (PK) at Day 0; specified collection of PK samples prior to Investigational medicinal product (IMP) dosing • Added requirement to Visit S3 (Week -1) that LDL-C ≥70 milligrams per deciliter (mg/dL) • Added chemistry panel and creatine kinase (CK) to Visit S3 (Week -1) given inclusion of ezetimibe naive participants • Removed optional genetic sampling • Removed instructions to reserve samples • Corrected windowing of allowable and prohibited medications to be consistent between entry criteria and protocol body • Removed lipids other than LDL-C as a specified tertiary endpoint • Removed manufacturing contact details (provided in pharmacy manual) • Added text on the administration of study-supplied ezetimibe, including assessment of relationship of adverse events (AEs) to both IMP and ezetimibe • Changed monitoring of CK for asymptomatic participants per FDA request • Revised safety endpoints • Revised statistical sections to clarify level of significance, standard deviation, methods for imputation of missing data, and application of analysis of covariance (ANCOVA) model for primary and secondary endpoints • Made administrative changes made throughout protocol where required to correct inconsistencies, add clarification, or correct errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29910030