



Clinical trial results:

A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy

Summary

EudraCT number	2016-003486-26
Trial protocol	DE GB
Global end of trial date	22 September 2018

Results information

Result version number	v1 (current)
This version publication date	09 October 2019
First version publication date	09 October 2019

Trial information

Trial identification

Sponsor protocol code	1002-047
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02991118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Esperion Therapeutics Inc.
Sponsor organisation address	3891 Ranchero Drive, Suite 150, Ann Arbor, Michigan, United States, 48108
Public contact	Director of Clinical Development, Esperion Therapeutics Inc., 00 1 7348873903, clinicaltrials@esperion.com
Scientific contact	Director of Clinical Development, Esperion Therapeutics Inc., 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	25 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the 12-week efficacy of bempedoic acid (ETC-1002) 180 milligrams (mg) per day versus placebo in decreasing low-density lipoprotein cholesterol (LDL-C) in high cardiovascular (CV) risk participants with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who were not adequately controlled with their maximally tolerated lipid-modifying therapy.

Protection of trial subjects:

This 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:

Participants were required to be on stable background lipid-modifying therapy (LMT), including a maximally tolerated statin, for at least 4 weeks prior to screening. Maximally tolerated statins included statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must have been documented. Stable LMT included, but was not limited to, monotherapies or combination therapies containing the following compounds: Statins (Atorvastatin [Lipitor®, Sortis®], Fluvastatin [Lescol®], Lovastatin [Mevacor®, Altoprev™], Pravastatin [Pravachol®], Pitavastatin [Livalo®, Lipostat®], Rosuvastatin [Crestor®], or Simvastatin [Zocor®] at average daily doses <40 mg); selective cholesterol and/or bile acid absorption inhibitors (Cholestyramine/Colestyramine [Questran®, Questran Light®, Prevalite®, Locholest®, Locholest® Light], Colestipol [Colestid®], Colesevelam hydrochloride [Welchol®, Cholestagel®], or Ezetimibe [Zetia®, Ezetrol®]); Fibrates (must have been stable at least 6 weeks prior to screening) (Fenofibrate [Antara®, Lofibra®, Tricor®, Triglide™, Lipantil®, Supralip®], Bezafibrate [Bezalip®], or Ciprofibrate [Modalim®]); PCSK9 inhibitors (Alirocumab [Praluent®], Evolocumab [Repatha®]); Other (Ezetimibe/simvastatin combinations where simvastatin doses were <40 mg/day [Vytorin® 10 mg/10 mg and 10 mg/20 mg, Inegy® 10 mg/20 mg], Atorvastatin/ezetimibe combinations [Atozet®]). An adjunctive therapy plan was in place for those participants whose low-density lipoprotein cholesterol (LDL-C) values met protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results were masked to investigators to ensure the blind was maintained; however, previously defined thresholds were set to notify investigators and provide an opportunity to adjust the participant's standard of care regimen.

Evidence for comparator: -

Actual start date of recruitment	18 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	Poland: 237
Country: Number of subjects enrolled	United Kingdom: 119
Country: Number of subjects enrolled	Germany: 78

Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Ukraine: 118
Country: Number of subjects enrolled	United States: 213
Worldwide total number of subjects	779
EEA total number of subjects	434

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)	379
From 65 to 84 years	395
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

A total of 779 participants were randomized 2:1 to receive either bempedoic acid or placebo.

Pre-assignment

Screening details:

The study consisted of 3 periods: a 1-week screening period; a 4-week single-blind, placebo run-in period; and a 52-week double-blind, randomized 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 (e.g., investigator, pharmacist), and other vendor personnel were blinded to the treatment group for each participant. Participants were also blinded to the treatment they received. Blinding of treatment was required to be maintained for all participants unless, in the opinion of the investigator, the safety of the participant might be at risk.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received placebo once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.

Arm type	Placebo
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 a placebo tablet once daily by mouth for 52 weeks during the double-blind treatment period.

Arm title	Bempedoic acid
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Arm description:

Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received a bempedoic acid 180 milligram (mg) tablet once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.

Arm type	Experimental
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 a bempedoic acid 180 mg tablet once daily by mouth for 52 weeks during the double-blind treatment period.

Number of subjects in period 1	Placebo	Bempedoic acid
Started	257	522
Completed	250	490
Not completed	7	32
Consent withdrawn by subject	1	7
Physician decision	-	1
Adverse event, non-fatal	2	2
Death	3	8
Could not attend study visits	-	1
Lost to follow-up	1	9
Moved out of the country	-	1
Protocol deviation	-	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received placebo once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.	
Reporting group title	Bempedoic acid
Reporting group description:	
Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received a bempedoic acid 180 milligram (mg) tablet once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.	

Reporting group values	Placebo	Bempedoic acid	Total
Number of subjects	257	522	779
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	64.7	64.1	
standard deviation	± 8.73	± 8.82	-
Gender categorical			
Units: Subjects			
Female	89	194	283
Male	168	328	496
Race			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	0	4	4
Black or African American	12	24	36
Native Hawaiian or Other Pacific Islander	0	1	1
White	244	491	735
Multiple	0	2	2
Mean low-density lipoprotein cholesterol (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.			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean	122.4	119.4	
standard deviation	± 38.30	± 37.75	-
Mean non-high-density lipoprotein cholesterol (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.			
Units: mg/dL			
arithmetic mean	153.7	150.7	
standard deviation	± 44.36	± 42.75	-

Mean total cholesterol (TC)			
Baseline was defined as the mean of the TC values from the last two non-missing values on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	204.8	202.1	
standard deviation	± 46.06	± 42.71	-
Mean apolipoprotein B (apoB)			
Baseline was defined as the last non-missing value on or prior to Day 1.			
Units: mg/dL			
arithmetic mean	118.6	116.2	
standard deviation	± 30.53	± 29.58	-
Mean high-sensitivity C-reactive protein (hsCRP)			
Baseline was defined as the last non-missing value on or prior to Day 1. Dispersion data are reported as the first quartile and third quartile values.			
Units: milligrams per Liter			
median	1.880	1.610	
inter-quartile range (Q1-Q3)	0.920 to 3.790	0.870 to 3.455	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received placebo once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.	
Reporting group title	Bempedoic acid
Reporting group description: Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received a bempedoic acid 180 milligram (mg) tablet once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.	

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: 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 is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.	
End point type	Primary
End point timeframe: Baseline; Week 12	

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253 ^[1]	498 ^[2]		
Units: percent change				
least squares mean (standard error)	2.35 (± 1.446)	-15.07 (± 1.073)		

Notes:

[1] - Full Analysis Set. Only those participants with available data were analyzed.

[2] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

Statistical analysis title	Difference [bempedoic acid - placebo] in LS mean
Statistical analysis description: The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval (CI) of 95%. Data were analyzed using analysis of covariance (ANCOVA), with treatment group and randomization stratification factors (cardiovascular risk and Baseline statin intensity) as factors and Baseline LDL-C as a covariate.	
Comparison groups	Bempedoic acid v Placebo

Number of subjects included in analysis	751
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-17.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.951
upper limit	-13.896
Variability estimate	Standard error of the mean
Dispersion value	1.8

Secondary: Percent change from baseline to Week 24 in LDL-C

End point title	Percent change from baseline to Week 24 in LDL-C
End point description:	
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 is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.	
End point type	Secondary
End point timeframe:	
Baseline; Week 24	

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247 ^[3]	485 ^[4]		
Units: percent change				
least squares mean (standard error)	2.66 (± 1.910)	-12.10 (± 1.479)		

Notes:

[3] - Full Analysis Set. Only those participants with available data were analyzed.

[4] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

Statistical analysis title	Difference [bempedoic acid - placebo] in LS mean
Statistical analysis description:	
The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a CI of 95%. Data were analyzed using ANCOVA, with treatment group and randomization stratification factors (cardiovascular risk and Baseline statin intensity) as factors and Baseline LDL-C as a covariate. Secondary endpoints were tested in a hierarchical analysis in the order they appear in this summary. Statistical significance at each step was required in order to test the next hypothesis.	
Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-14.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.504
upper limit	-10.027
Variability estimate	Standard error of the mean
Dispersion value	2.418

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:	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 is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.
End point type	Secondary
End point timeframe:	Baseline; Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253 ^[5]	498 ^[6]		
Units: percent change				
least squares mean (standard error)	2.28 (± 1.351)	-10.75 (± 0.952)		

Notes:

[5] - Full Analysis Set. Only those participants with available data were analyzed.

[6] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

Statistical analysis title	Difference [bempedoic acid - placebo] in LS mean
Statistical analysis description:	The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a CI of 95%. Data were analyzed using ANCOVA, with treatment group and randomization stratification factors (cardiovascular risk and Baseline statin intensity) as factors and Baseline non-HDL-C as a covariate. Secondary endpoints were tested in a hierarchical analysis in the order they appear in this summary. Statistical significance at each step was required in order to test the next hypothesis.
Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	751
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-13.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.27
upper limit	-9.794
Variability estimate	Standard error of the mean
Dispersion value	1.652

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:	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 is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.
End point type	Secondary
End point timeframe:	Baseline; Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253 ^[7]	499 ^[8]		
Units: percent change				
least squares mean (standard error)	1.26 (± 1.010)	-9.94 (± 0.688)		

Notes:

[7] - Full Analysis Set. Only those participants with available data were analyzed.

[8] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

Statistical analysis title	Difference [bempedoic acid - placebo] in LS mean
Statistical analysis description:	The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a CI of 95%. Data were analyzed using ANCOVA, with treatment group and randomization stratification factors (cardiovascular risk and Baseline statin intensity) as factors and Baseline TC as a covariate. Secondary endpoints were tested in a hierarchical analysis in the order they appear in this summary. Statistical significance at each step was required in order to test the next hypothesis.
Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	752
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.599
upper limit	-8.801
Variability estimate	Standard error of the mean
Dispersion value	1.224

Secondary: Percent change from baseline to Week 12 in apolipoprotein b (apo B)

End point title	Percent change from baseline to Week 12 in apolipoprotein b (apo B)
End point description: Baseline for apo B was defined as the last non-missing value on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.	
End point type	Secondary
End point timeframe: Baseline; Week 12	

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245 ^[9]	479 ^[10]		
Units: percent change				
least squares mean (standard error)	3.73 (± 1.340)	-9.29 (± 0.851)		

Notes:

[9] - Full Analysis Set. Only those participants with available data were analyzed.

[10] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

Statistical analysis title	Difference [bempedoic acid - placebo] in LS mean
Statistical analysis description: The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a CI of 95%. Data were analyzed using ANCOVA, with treatment group and randomization stratification factors (cardiovascular risk and Baseline statin intensity) as factors and Baseline apo B as a covariate. Secondary endpoints were tested in a hierarchical analysis in the order they appear in this summary. Statistical significance at each step was required in order to test the next hypothesis.	
Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	724
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-13.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.13
upper limit	-9.907
Variability estimate	Standard error of the mean
Dispersion value	1.587

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: Baseline for hsCRP was defined as the last non-missing value on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants. The Q3 value reported represents the actual interquartile range (calculated as the third quartile [Q3] value minus the first quartile [Q1] value). -99999 is a null value and serves as a placeholder.	
End point type	Secondary
End point timeframe: Baseline; Week 12	

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240 ^[11]	467 ^[12]		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-9.366 (-99999 to 71.561)	-18.699 (-99999 to 69.931)		

Notes:

[11] - Full Analysis Set. Only those participants with available data were analyzed.

[12] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

Statistical analysis title	Wilcoxon Two Sample Test
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Statistical analysis description:

The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a CI of 95%. A nonparametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval was performed. Secondary endpoints were tested in a hierarchical analysis in the order they appear in this summary. Statistical significance at each step was required in order to test the next hypothesis.

Comparison groups	Placebo v Bempedoic acid
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.039
Method	Wilcoxon Two Sample Test
Parameter estimate	Location shift
Point estimate	-8.733
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.238
upper limit	-0.434

Secondary: Change from baseline to Week 12 in LDL-C

End point title	Change from baseline to Week 12 in LDL-C
End point description:	Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Change from Baseline is calculated as the post-baseline value minus the baseline value. The Full Analysis Set was comprised of all randomized participants. Analysis was conducted using descriptive statistics by treatment group using observed data.
End point type	Secondary
End point timeframe:	Baseline; Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253 ^[13]	498 ^[14]		
Units: mg/dL				
arithmetic mean (standard deviation)	0.0 (± 30.62)	-21.2 (± 30.82)		

Notes:

[13] - Full Analysis Set. Only those participants with available data were analyzed.

[14] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 24 in LDL-C

End point title	Change from baseline to Week 24 in LDL-C
End point description:	Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Change from Baseline is calculated as the post-baseline value minus the baseline value. The Full Analysis Set was comprised of all randomized participants. Analysis was conducted using descriptive statistics by treatment group using observed data.
End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247 ^[15]	485 ^[16]		
Units: mg/dL				
arithmetic mean (standard deviation)	-1.0 (± 37.51)	-18.7 (± 35.76)		

Notes:

[15] - Full Analysis Set. Only those participants with available data were analyzed.

[16] - Full Analysis Set. Only those participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to Week 52

Adverse event reporting additional description:

Treatment-emergent events, defined as those adverse events that began or worsened after the first dose of investigational medicinal product (IMP) until 30 days after the last dose of IMP, were collected and reported. The analysis was performed using the Safety Analysis Set, comprised of all randomized participants who received ≥ 1 dose of IMP.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received placebo once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.

Reporting group title	Bempedoic acid
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Reporting group description:

Participants received a placebo tablet once daily by mouth for 4 weeks prior to the 52-week double-blind treatment period. During the treatment period, participants received a bempedoic acid 180 milligram (mg) tablet once daily by mouth for 52 weeks. Participants remained on ongoing lipid-modifying therapy (not study provided) throughout the study.

Serious adverse events	Placebo	Bempedoic acid	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 257 (18.68%)	106 / 522 (20.31%)	
number of deaths (all causes)	2	6	
number of deaths resulting from adverse events	2	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			

subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour of the lung			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			

subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 257 (0.39%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery thrombosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Supportive care			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 257 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Exercise tolerance decreased			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 257 (0.78%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent occlusion			
subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 257 (1.56%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Brain contusion			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas poisoning			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Kidney rupture			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thoracic procedure complication			

subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 257 (0.00%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 257 (1.17%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 257 (0.39%)	12 / 522 (2.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	6 / 257 (2.33%)	9 / 522 (1.72%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 257 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 257 (0.39%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 257 (0.78%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 257 (0.78%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 257 (0.39%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 257 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			

subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	6 / 257 (2.33%)	7 / 522 (1.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 257 (0.78%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	4 / 257 (1.56%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			

subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyporeflexia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 257 (0.78%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post stroke epilepsy			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 257 (0.00%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Microcytic anaemia			

subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			

subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal adhesions			

subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 257 (0.39%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephritis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary incontinence			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
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			
Back pain			
subjects affected / exposed	0 / 257 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 257 (0.78%)	5 / 522 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periostitis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spondylitis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 257 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 257 (0.39%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urethral stricture post infection			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 257 (0.00%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			

subjects affected / exposed	0 / 257 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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	88 / 257 (34.24%)	211 / 522 (40.42%)	
Investigations			
Blood uric acid increased			
subjects affected / exposed	1 / 257 (0.39%)	14 / 522 (2.68%)	
occurrences (all)	1	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 257 (2.33%)	7 / 522 (1.34%)	
occurrences (all)	6	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 257 (3.50%)	8 / 522 (1.53%)	
occurrences (all)	9	10	
Headache			
subjects affected / exposed	7 / 257 (2.72%)	10 / 522 (1.92%)	
occurrences (all)	7	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 257 (1.17%)	14 / 522 (2.68%)	
occurrences (all)	3	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 257 (3.50%)	6 / 522 (1.15%)	
occurrences (all)	10	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 257 (2.72%)	16 / 522 (3.07%)	
occurrences (all)	8	18	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	8 / 257 (3.11%)	18 / 522 (3.45%)	
occurrences (all)	8	19	
Muscle spasms			
subjects affected / exposed	3 / 257 (1.17%)	11 / 522 (2.11%)	
occurrences (all)	3	12	
Myalgia			
subjects affected / exposed	8 / 257 (3.11%)	15 / 522 (2.87%)	
occurrences (all)	8	15	
Osteoarthritis			
subjects affected / exposed	3 / 257 (1.17%)	11 / 522 (2.11%)	
occurrences (all)	4	11	
Pain in extremity			
subjects affected / exposed	1 / 257 (0.39%)	11 / 522 (2.11%)	
occurrences (all)	1	11	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 257 (2.33%)	7 / 522 (1.34%)	
occurrences (all)	7	7	
Lower respiratory tract infection			
subjects affected / exposed	7 / 257 (2.72%)	7 / 522 (1.34%)	
occurrences (all)	7	9	
Nasopharyngitis			
subjects affected / exposed	13 / 257 (5.06%)	27 / 522 (5.17%)	
occurrences (all)	15	31	
Upper respiratory tract infection			
subjects affected / exposed	9 / 257 (3.50%)	19 / 522 (3.64%)	
occurrences (all)	10	20	
Urinary tract infection			
subjects affected / exposed	5 / 257 (1.95%)	24 / 522 (4.60%)	
occurrences (all)	5	28	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	6 / 257 (2.33%)	10 / 522 (1.92%)	
occurrences (all)	6	11	
Gout			

subjects affected / exposed	2 / 257 (0.78%)	11 / 522 (2.11%)	
occurrences (all)	2	11	
Hyperuricaemia			
subjects affected / exposed	5 / 257 (1.95%)	22 / 522 (4.21%)	
occurrences (all)	5	22	
Type 2 diabetes mellitus			
subjects affected / exposed	7 / 257 (2.72%)	10 / 522 (1.92%)	
occurrences (all)	7	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2017	Major changes to the protocol included revision of the definition of true abstinence in the Inclusion Criteria.
22 March 2017	Major changes to the protocol included: (a) updated text pertaining to the bempedoic acid mechanism of action based on new information; (b) reduced planned enrollment; (c) removed the requirement that strata (statin dose and participant status) could not be capped in order to ensure adequate number of participant characteristics if imbalance occurred; (d) revised secondary and tertiary endpoints as well as added safety endpoints; (e) added additional clinical and telephone visits for participants taking simvastatin 40 milligrams (mg); (f) added implantable, injectable, or topical method as allowable forms of hormonal contraception; (g) added requirement that women use 2 rather than 1 form of acceptable contraception; (h) added additional fasting LDL-C assessment after the Run-in period to Inclusion Criteria. Removed the allowance of repeating a screening LDL-C measurement after Visit S1; (i) clarified the timing of the collection of lipid values; (j) further defined Inclusion Criteria around PAD and cerebrovascular atherosclerotic disease; (j) added eGFR <45 mL/min/1.73 m ² in participants taking simvastatin as exclusionary; (k) excluded participants who have enrolled in a study of an experimental siRNA inhibitor of PCSK9; (l) clarified time period during which participants should not intend to become pregnant; (m) altered the 3-month time period for not using the certain drugs prior to screening; (n) removed collection of optional genetic sampling, reserve samples, and PK sample collection on Day 1; (o) added windows to all visits; (p) removed manufacturing contact details; (q) modified the monitoring and management of CK values for asymptomatic participants; (r) revised statistical sections; (s) added details to clarify the time period and reporting process for the collection of adverse events; (t) added sections related to adverse events; (u) made administrative changes where required to correct inconsistencies, add clarification, or correct errors.
09 May 2017	Major changes to the protocol included: (a) Simvastatin at average daily doses of 40 mg or greater was added as a prohibited medication. The protocol was amended to remove study visits at Weeks 16, 20, 28, and 32 that were only for participants taking simvastatin 40 mg/day. A letter was provided to all investigators with instructions on how to proceed for enrolled participants receiving simvastatin 40 mg/day. (b) Increased number of participants to be enrolled from approximately 525 to approximately 750 participants (500 bempedoic acid; 250 placebo), as was included in the original protocol and Amendment 1. The reason for the increase in participants was due to the decision to discontinue investigational medicinal product in participants receiving simvastatin at average daily doses ≥40 mg across the bempedoic acid program, therefore resulting in an overall smaller safety database than planned. Based on this decision, the sample size in this study was increased back to the original sample size of 750 participants to ensure the safety database was sufficiently large for an approval of a low-density lipoprotein cholesterol (LDL-C) lowering indication. (c) Clarified that the requirement to have ≥80% treatment compliance during the Run-in Period refers to the average treatment compliance over the entire Run-in Period (compliance measured at Visits S3 and T1). (d) Corrected the visit window for Week 24 within the protocol text and Appendix 1, Schedule of Events, to reflect 168 ± 7 days. (d) Updated the definition of serious adverse events to include hospitalizations for preplanned surgeries and/or elective surgeries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported