Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Long-Term Safety and Tolerability Study of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Summary

EudraCT number	2015-004136-36
Trial protocol	NL GB DE PL
Global end of trial date	21 February 2018

Results information

Result version number	v1 (current)
This version publication date	12 April 2019
First version publication date	12 April 2019

Trial information

Trial identification

Sponsor protocol code	1002-040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02666664
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, United States, 48108
Public contact	Director of Clinical Operations, Esperion Therapeutics, 001 7348873903, clinicaltrials@esperion.com
Scientific contact	Director of Clinical Operations, Esperion Therapeutics, 001 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	28 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study was to evaluate the long-term safety and tolerability of ETC-1002 versus placebo 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, including maximally tolerated statin therapy.

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:

Participants were required to be on stable lipid-modifying therapy (ies), including a maximally tolerated statin for at least 4 weeks prior to screening. Use of fibrates must have been stable at least 6 weeks prior to screening. Stable lipid-modifying therapy(s) 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®), Simvastatin (Zocor® or Vytorin® or Inegy® where simvastatin dose was less than 40 mg), Rosuvastatin (Crestor®)]; 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 [Fenofibrate (Antara®, Lofibra®, Tricor®, Triglide™, Lipantil®, Supralip®), Bezafibrate (Bezalip®), or Ciprofibrate (Modalim®)]; Approved PCSK9 inhibitors were excluded at entry criteria but allowed as adjunctive therapy beginning at Week 24 if LDL-C threshold criteria was met as described in the protocol. Gemfibrozil, a fibrate, was prohibited. Other concomitant medications were allowed but must have been stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety. Participants were not allowed to use some medications (monotherapies or combination therapies) within 4 weeks prior to screening or during the study.

Evidence for comparator:

The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid lowering therapy design was added to ensure that long-term safety data are meaningful and interpretable.

Actual start date of recruitment	21 January 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	Germany: 269
Country: Number of subjects enrolled	Netherlands: 162
Country: Number of subjects enrolled	Poland: 571
Country: Number of subjects enrolled	United Kingdom: 462

Country: Number of subjects enrolled	United States: 560
Country: Number of subjects enrolled	Canada: 206
Worldwide total number of subjects	2230
EEA total number of subjects	1464

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)	877
From 65 to 84 years	1333
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

A total of 2230 participants were randomized 2:1 to either bempedoic acid or placebo. One participant was randomized to bempedoic acid treatment, but never received any dose of investigational medicinal product (IMP) i.e. study drug.

Pre-assignment

Screening details:

The study consisted of 2 periods: a 2-week screening 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	Investigator, Monitor, Data analyst, Subject, Carer, Assessor

Blinding implementation details:

The Sponsor, all clinical site personnel (eg, investigator, pharmacist, and laboratory personnel), 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 participants might have been at risk.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

During the double-blind treatment period, participants received placebo tablet, once daily by mouth for 52 weeks. In addition, participants received stable background lipid-modifying therapy(ies) including a maximally tolerated statin 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 placebo tablet, once-daily by mouth for 52 weeks during the double-blind treatment period.

Arm title	Bempedoic acid

Arm description:

During the double-blind treatment period, participants received bempedoic acid 180 mg tablet, once daily by mouth for 52 weeks. In addition, participants received stable background lipid-modifying therapy(ies) including a maximally tolerated statin 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 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	742	1488
Completed	706	1404
Not completed	36	84
Physician decision	-	1
Adverse event, non-fatal	12	37
Protocol violation	-	2
Withdrawal by participant	23	40
Unknown	-	1
Lost to follow-up	1	2
Sponsor decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
During the double-blind treatment period, participants received placebo tablet, once daily by mouth for 52 weeks. In addition, participants received stable background lipid-modifying therapy(ies) including a maximally tolerated statin throughout the study.	
Reporting group title	Bempedoic acid
Reporting group description:	
During the double-blind treatment period, participants received bempedoic acid 180 mg tablet, once daily by mouth for 52 weeks. In addition, participants received stable background lipid-modifying therapy(ies) including a maximally tolerated statin throughout the study.	

Reporting group values	Placebo	Bempedoic acid	Total
Number of subjects	742	1488	2230
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.8	65.8	
standard deviation	± 8.64	± 9.11	-
Gender categorical Units: Subjects			
Female	213	389	602
Male	529	1099	1628
Race Units: Subjects			
American Indian or Alaska Native	1	2	3
Asian	8	14	22
Native Hawaiian or Other Pacific Islander	0	2	2
Black or African American	15	42	57
White	716	1423	2139
More than one race	0	1	1
Unknown or Not Reported	2	4	6
Ethnicity Units: Subjects			
Hispanic or Latino	11	24	35
Not Hispanic or Latino	731	1464	2195
Unknown or Not Reported	0	0	0
Cardiovascular history: atherosclerotic cardiovascular disease (ASCVD) Units: Subjects			
Yes	727	1449	2176
No	15	39	54
Cardiovascular history: heterozygous familial hypercholesterolemia (HeFH) Units: Subjects			
Yes	23	56	79

No	719	1432	2151
History of diabetes Units: Subjects			
Yes	212	425	637
No	530	1063	1593
History of hypertension Units: Subjects			
Yes	594	1174	1768
No	148	314	462
Concomitant lipid-modifying therapy (LMT): Statin			
Concomitant medications are defined as medications that were ongoing at the time of double-blind study drug initiation or new medications that started post double-blind study drug initiation and within 30 days following the date of the last dose of study drug.			
Units: Subjects			
Yes	742	1485	2227
No	0	3	3
Concomitant LMT: Ezetimibe			
Concomitant medications are defined as medications that were ongoing at the time of double-blind study drug initiation or new medications that started post double-blind study drug initiation and within 30 days following the date of the last dose of study drug.			
Units: Subjects			
Yes	56	116	172
No	686	1372	2058
Concomitant LMT: Fibrate			
Concomitant medications are defined as medications that were ongoing at the time of double-blind study drug initiation or new medications that started post double-blind study drug initiation and within 30 days following the date of the last dose of study drug.			
Units: Subjects			
Yes	26	54	80
No	716	1434	2150
Concomitant LMT: None			
Concomitant medications are defined as medications that were ongoing at the time of double-blind study drug initiation or new medications that started post double-blind study drug initiation and within 30 days following the date of the last dose of study drug.			
Units: Subjects			
Concomitant LMT: None	0	2	2
Concomitant LMT: Yes	742	1486	2228
Baseline statin intensity			
Baseline statin intensity were based on stratification at randomization.			
Units: Subjects			
Low	48	100	148
Moderate	324	646	970
High	370	742	1112
Estimated glomerular filtration rate (eGFR)			
milliliter per minute per 1.73 square meter = ml/min/1.73m^2			
Units: Subjects			
Normal: ≥ 90 mL/min/1.73m^2	167	320	487
Mild Renal Impairment: 60-89 mL/min/1.73m^2	468	946	1414
Moderate Renal Impairment: 30-59 mL/min/1.73m^2	107	222	329

Total cholesterol (TC)			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
arithmetic mean	178.64	179.66	
standard deviation	± 35.645	± 35.143	-
Low-density lipoprotein cholesterol (LDL-C)			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
arithmetic mean	102.30	103.60	
standard deviation	± 30.048	± 29.127	-
High-density lipoprotein cholesterol (HDL-C)			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
arithmetic mean	49.29	48.71	
standard deviation	± 11.545	± 11.853	-
Triglycerides (TG)			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
median	122.50	126.25	
inter-quartile range (Q1-Q3)	95.50 to 169.50	98.00 to 165.50	-
Non-high-density lipoprotein cholesterol (non-HDL-C)			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
arithmetic mean	129.37	130.92	
standard deviation	± 33.855	± 33.677	-
Apolipoprotein B (apoB)			
Baseline was defined as the last value prior to first dose of study drug.			
Units: mg/dL			
arithmetic mean	86.8	88.5	
standard deviation	± 21.82	± 21.57	-
High-sensitivity C-reactive protein (hsCRP)			
Baseline was defined as the last value prior to the first dose of study drug.			
Units: mg/L			
median	1.51	1.49	
inter-quartile range (Q1-Q3)	0.79 to 3.33	0.74 to 3.28	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

During the double-blind treatment period, participants received placebo tablet, once daily by mouth for 52 weeks. In addition, participants received stable background lipid-modifying therapy(ies) including a maximally tolerated statin throughout the study.

Reporting group title	Bempedoic acid

Reporting group description:

During the double-blind treatment period, participants received bempedoic acid 180 mg tablet, once daily by mouth for 52 weeks. In addition, participants received stable background lipid-modifying therapy(ies) including a maximally tolerated statin throughout the study.

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

End point title	Percentage of Participants With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

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

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[2]	1487[3]		
Units: percentage of participants				
number (not applicable)				
Any TEAE	78.7	78.5		
Any serious TEAE	14.0	14.5		
Any fatal TEAE	0.3	0.9		
Any TEAE leading to discontinuation of study drug	7.1	10.9		

Notes:

[2] - Safety Population (SP) included all randomized patients who received at least 1 dose of study drug.

[3] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Adjudicated Major Adverse Cardiovascular Event

End point title	Percentage of Participants With Adjudicated Major Adverse

	Cardiovascular Event[4]

End point description:

TEAEs, defined as AEs that began or worsened in severity after the first dose of double-blind study drug and up to 30 days after receiving the last dose of double-blind study drug, were collected and reported. Cardiovascular events were considered as adverse events of special interest. Treatment-emergent = TE.

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[5]	1487[6]		
Units: percentage of participants				
number (not applicable)				
Any adjudicated major clinical event	5.7	4.6		
Any TE death from cardiovascular causes	0.1	0.4		
Any nonfatal myocardial infarction	1.8	1.3		
Any nonfatal stroke	0.3	0.3		
Any coronary revascularization	3.2	2.6		
Any hospitalization for unstable angina	1.5	0.9		
TE death from noncardiovascular causes	0.1	0.1		
Noncoronary arterial revascularization	0.8	0.3		
Hospitalization for heart failure	0.1	0.6		

Notes:

[5] - SP

[6] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Creatine Kinase Elevations

End point title	Percentage of Participants With the Indicated Event of Special Interest: Creatine Kinase Elevations[7]

End point description:

TEAEs of special interest (AESIs) were predefined and monitored throughout the study. Creatine kinase elevations were assessed using the following preferred term: Blood creatine phosphokinase increased (system organ class: investigations).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[8]	1487[9]		
Units: percentage of participants				
number (not applicable)				
Blood creatine phosphokinase increased	1.8	2.4		

Notes:

[8] - SP

[9] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Hepatic Disorders

End point title	Percentage of Participants With the Indicated Event of Special Interest: Hepatic Disorders[10]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. TEAEs potentially related to hepatic events were assessed using the following preferred terms and laboratory abnormalities: aspartate aminotransferase (AST) increased, Alanine aminotransferase (ALT) increased, Hepatic enzyme increased, Blood bilirubin increased, liver function test abnormal, liver function test increased, hepatic enzyme abnormal, transaminases increased, potential Hy's Law cases (PHLC) [AST and (&)/or ALT >3 x upper limit of normal (ULN) with concurrent total bilirubin >2 x ULN], AST and/or ALT >3 x ULN, and total bilirubin >2 x ULN (system organ class: investigations).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[11]	1487[12]		
Units: percentage of participants				
number (not applicable)				
Overall hepatic disorder AESIs	1.5	2.5		
AST increased	0.4	1.5		
ALT increased	0.3	0.9		
Hepatic enzyme increased	0.0	0.5		
Blood bilirubin increased	0.4	0.1		
Liver function test abnormal	0.3	0.1		
Liver function test increased	0.1	0.2		
Hepatic enzyme abnormal	0.0	0.1		
Transaminases increased	0.1	0.0		
PHLC [AST &/or ALT>3 x ULN, concurrent TB>2 x ULN]	0.0	0.0		
AST and/or ALT >3 x ULN	0.1	0.5		
Total bilirubin >2 x ULN	0.0	0.0		

Notes:

[11] - SP

[12] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Hypoglycemia

End point title	Percentage of Participants With the Indicated Event of Special Interest: Hypoglycemia[13]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. Hypoglycemia was assessed using the following preferred terms: hypoglycaemia (system organ class: metabolism and nutrition disorders); blood glucose abnormal and blood glucose decreased (system organ class: investigations).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[14]	1487[15]		
Units: percentage of participants				
number (not applicable)				
Overall hypoglycemia AESIs	3.1	2.2		
Hypoglycaemia	3.0	2.2		
Blood glucose abnormal	0.1	0.1		
Blood glucose decreased	0.0	0.1		

Notes:

[14] - SP

[15] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Metabolic Acidosis

End point title	Percentage of Participants With the Indicated Event of Special Interest: Metabolic Acidosis[16]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. Metabolic acidosis was assessed using the preferred term metabolic acidosis (system organ class: metabolism and nutrition disorders).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[17]	1487[18]		
Units: percentage of participants				
number (not applicable)				
Metabolic acidosis	0.0	0.1		

Notes:

[17] - SP

[18] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Muscular Disorder

End point title	Percentage of Participants With the Indicated Event of Special Interest: Muscular Disorder[19]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. Muscular safety was assessed using the following preferred terms and laboratory abnormalities: myalgia, muscle spasms, pain in extremity, muscular weakness, and creatine kinase >5 ULN (system organ class: musculoskeletal and connective tissue disorders).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[20]	1487[21]		
Units: percentage of participants				
number (not applicable)				
Overall muscular disorder AESIs	10.1	13.1		
Myalgia	6.1	6.0		
Muscle spasms	2.7	4.2		
Pain in extremity	2.2	3.4		
Muscular weakness	0.5	0.6		
Creatine kinase >5 ULN	0.1	0.5		

Notes:

[20] - SP

[21] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Neurocognitive Disorder

End point title	Percentage of Participants With the Indicated Event of Special Interest: Neurocognitive Disorder[22]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. Neurocognitive disorder was assessed using the following preferred terms: memory impairment, amnesia, and cognitive disorder (system organ class: nervous system disorders); confusional state and disorientation (system organ class: psychiatric disorders).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[23]	1487[24]		
Units: percentage of participants				
number (not applicable)				
Overall neurocognitive disorder AESIs	0.9	0.7		
Memory impairment	0.5	0.3		
Amnesia	0.4	0.2		
Cognitive disorder	0.0	0.1		
Confusional state	0.0	0.1		
Disorientation	0.0	0.1		

Notes:

[23] - SP

[24] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: New Onset or Worsening Diabetes Mellitus

End point title	Percentage of Participants With the Indicated Event of Special Interest: New Onset or Worsening Diabetes Mellitus[25]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. New onset or worsening diabetes was assessed using the following preferred terms: type 2 diabetes mellitus, diabetes mellitus, hyperglycaemia, glucose tolerance impaired, diabetes mellitus inadequate control, and impaired fasting glucose (system organ class: metabolism and nutrition disorders); blood glucose increased, glycosylated haemoglobin increased, blood glucose abnormal, and glucose urine present (system organ class: investigations); and glycosuria (system organ class: renal and urinary disorders).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[26]	1487[27]		
Units: percentage of participants				
number (not applicable)				
Overall new onset/worsening diabetes mellitus AESI	5.4	3.3		
Type 2 diabetes mellitus	0.9	1.0		
Diabetes mellitus	0.9	0.4		
Hyperglycaemia	0.7	0.5		
Glucose tolerance impaired	0.1	0.4		
Diabetes mellitus inadequate control	0.4	0.1		
Impaired fasting glucose	0.3	0.1		
Blood glucose increased	1.2	0.7		
Glycosylated haemoglobin increased	0.5	0.0		
Blood glucose abnormal	0.1	0.1		
Glucose urine present	0.1	0.0		
Glycosuria	0.3	0.1		

Notes:

[26] - SP

[27] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With the Indicated Event of Special Interest: Renal Disorder

End point title	Percentage of Participants With the Indicated Event of Special Interest: Renal Disorder[28]

End point description:

Treatment-emergent AESIs were predefined and monitored throughout the study. TEAEs potentially related to renal events were assessed using the following preferred terms: renal failure, renal impairment, acute kidney injury (system organ class: renal and urinary disorders); blood creatinine increased, glomerular filtration rate decreased, blood urea increased, estimated glomerular filtration rate (eGFR) <30 milliliter per minute per 1.73 square meter (ml/min/1.73m^2), and change from baseline in creatinine >1 mg/dL (system organ class: investigations); and gout (system organ class: metabolism and nutrition disorders).

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[29]	1487[30]		
Units: percentage of participants				
number (not applicable)				
Renal failure	0.1	0.9		
Renal impairment	0.1	0.4		
Acute kidney injury	0.3	0.3		
Blood creatinine increased	0.4	0.8		
Glomerular filtration rate decreased	0.0	0.5		
Blood urea increased	0.1	0.1		
Gout	0.3	1.2		
Change from baseline in creatinine >1 mg/dL	0.0	0.1		
eGFR <30 mL/min/1.73 m^2	0.4	0.9		

Notes:

[29] - SP

[30] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Week 52 in Uric Acid Level

End point title	Change From Baseline to Week 52 in Uric Acid Level[31]

End point description:

Blood samples were drawn at defined time points during the course of the study to monitor uric acid levels.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[32]	1487[33]		
Units: milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Baseline	5.96 (± 1.35)	6.06 (± 1.37)		
Change from Baseline at Week 52	-0.06 (± 0.87)	0.73 (± 1.11)		

Notes:

[32] - SP

[33] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Week 52 in Creatinine Level

End point title	Change From Baseline to Week 52 in Creatinine Level[34]

End point description:

Blood samples were drawn at defined time points during the course of the study to monitor creatinine levels.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[35]	1487[36]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	0.96 (± 0.22)	0.97 (± 0.22)		
Change from Baseline at Week 52	-0.02 (± 0.12)	0.02 (± 0.13)		

Notes:

[35] - SP

[36] - SP

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Week 52 in Hemoglobin Level

End point title	Change From Baseline to Week 52 in Hemoglobin Level[37]

End point description:

Blood samples were drawn at defined time points during the course of the study to monitor hemoglobin levels.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis was descriptive in nature.

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[38]	1487[39]		
Units: grams per deciliter (g/dL)				
arithmetic mean (standard deviation)				
Baseline	14.07 (± 1.26)	14.22 (± 1.26)		
Change from Baseline at Week 52	-0.23 (± 0.85)	-0.58 (± 0.88)		

Notes:

[38] - SP

[39] - SP

Statistical analyses

No statistical analyses for this end point

Secondary: 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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(LDL-C value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen. Least Square mean= LS mean.

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	742[40]	1488[41]		
Units: percent change				
least squares mean (standard error)	1.6 (± 0.86)	-16.5 (± 0.52)		

Notes:

[40] - Full Analysis Set (FAS) included all randomized participants

[41] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 12

Statistical analysis description:

The percentage change from baseline were analyzed with the use of analysis of covariance (ANCOVA), with treatment group and randomization strata as factors and baseline lipid value as a covariate.

Comparison groups	Placebo v Bempedoic acid
Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	-16.1
Variability estimate	Standard error of the mean
Dispersion value	1.01

Secondary: Absolute Change From Baseline to Week 12 in LDL-C

End point title	Absolute Change From Baseline to Week 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 analyzed for LDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Absolute change from baseline was calculated as: LDL-C value at Week 12 minus Baseline value. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen.

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	742[42]	1488[43]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 12 (n = 725, 1424)	0.43 (± 27.036)	-19.23 (± 24.005)		

Notes:

[42] - FAS

[43] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 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:

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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(LDL-C value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen.

End point type	Other pre-specified

End point timeframe:

Week 24

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[44]	1488[45]		
Units: percent change				
least squares mean (standard error)	1.2 (± 0.88)	-14.9 (± 0.60)		

Notes:

[44] - FAS

[45] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 24

Statistical analysis description:

The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate.

Comparison groups	Placebo v Bempedoic acid
Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.2
upper limit	-14
Variability estimate	Standard error of the mean
Dispersion value	1.07

Other pre-specified: 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 analyzed for non-HDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(non-HDL-C value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen.

End point type	Other pre-specified

End point timeframe:

Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[46]	1488[47]		
Units: percent change				
least squares mean (standard error)	1.5 (± 0.76)	-11.9 (± 0.48)		

Notes:

[46] - FAS

[47] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 12

Statistical analysis description:

The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate.

Comparison groups	Placebo v Bempedoic acid
Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.1
upper limit	-11.6
Variability estimate	Standard error of the mean
Dispersion value	0.9

Other pre-specified: 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 analyzed for TC. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(TC value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen.

End point type	Other pre-specified

End point timeframe:

Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[48]	1488[49]		
Units: percent change				
least squares mean (standard error)	0.8 (± 0.57)	-10.3 (± 0.37)		

Notes:

[48] - FAS

[49] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 12

Statistical analysis description:

The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and

randomization strata as factors and baseline lipid value as a covariate.

Comparison groups	Bempedoic acid v Placebo
Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.5
upper limit	-9.8
Variability estimate	Standard error of the mean
Dispersion value	0.69

Other pre-specified: 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 analyzed for apoB. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(apoB value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen

End point type	Other pre-specified

End point timeframe:

Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[50]	1488[51]		
Units: percent change				
least squares mean (standard error)				
Week 12 (n = 736, 1485)	3.3 (± 0.70)	-8.6 (± 0.47)		

Notes:

[50] - FAS

[51] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 12

Statistical analysis description:

The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate.

Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	-10.2
Variability estimate	Standard error of the mean
Dispersion value	0.85

Other pre-specified: 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 analyzed for hsCRP. Baseline was defined as the last value prior to first dose of IMP. Percent change from baseline was calculated as: [(hsCRP value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 12

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[52]	1488[53]		
Units: percent change				
least squares mean (standard error)				
Week 12 (n = 724, 1421)	2.6 (± 91.9)	-22.4 (± 72.5)		

Notes:

[52] - FAS

[53] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 12

Statistical analysis description:

The percentage change from baseline was analyzed with the use of a nonparametric approach, P values are from the Wilcoxon rank-sum test, and location shift and confidence interval from the Hodges-Lehmann estimates.

Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Location shift
Point estimate	-21.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.96
upper limit	-16
Variability estimate	Standard error of the mean
Dispersion value	2.8

Other pre-specified: Percent Change From Baseline to Week 52 in LDL-C

End point title	Percent Change From Baseline to Week 52 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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(LDL-C value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 52

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[54]	1488[55]		
Units: percent change				
least squares mean (standard error)				
Week 52 (n = 685, 1364)	1.0 (± 0.92)	-12.6 (± 0.66)		

Notes:

[54] - FAS

[55] - FAS

Statistical analyses

Statistical analysis title	Difference [BA - placebo] in LS mean at Week 52

Statistical analysis description:

The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate.

Comparison groups	Placebo v Bempedoic acid

Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	-11.3
Variability estimate	Standard error of the mean
Dispersion value	1.13

Other pre-specified: Percent Change From Baseline to Week 24 in non-HDL-C

End point title	Percent Change From Baseline to Week 24 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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(non-HDL-C value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 24

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[56]	1488[57]		
Units: percent change				
arithmetic mean (standard deviation)				
Week 24 (n = 707, 1396)	1.61 (± 20.914)	-11.69 (± 19.800)		

Notes:

[56] - FAS

[57] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 52 in non-HDL-C

End point title	Percent Change From Baseline to Week 52 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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(non-HDL-C

value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 52

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[58]	1488[59]		
Units: percent change				
arithmetic mean (standard deviation)				
Week 52 (n = 685, 1364)	0.65 (± 21.438)	-10.07 (± 22.097)		

Notes:

[58] - FAS

[59] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 24 in TC

End point title	Percent Change From Baseline to Week 24 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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(TC value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 24

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[60]	1488[61]		
Units: percent change				
arithmetic mean (standard deviation)				
Week 24 (n = 708, 1396)	1.15 (± 15.349)	-9.86 (± 15.358)		

Notes:

[60] - FAS

[61] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 52 in TC

End point title	Percent Change From Baseline to Week 52 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 values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(TC value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 52

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[62]	1488[63]		
Units: percent change				
arithmetic mean (standard deviation)				
Week 52 (n = 685, 1365)	0.38 (± 16.180)	-8.92 (± 16.945)		

Notes:

[62] - FAS

[63] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 24 in apoB

End point title	Percent Change From Baseline to Week 24 in 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 analyzed for apoB. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(apoB value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed

End point type	Other pre-specified

End point timeframe:

Week 24

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[64]	1488[65]		
Units: percent change				
arithmetic mean (standard deviation)				
Week 24 (n = 699, 1381)	4.8 (± 20.41)	-7.1 (± 20.01)		

Notes:
[64] - FAS
[65] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 52 in apoB

End point title	Percent Change From Baseline to Week 52 in 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 analyzed for apoB. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(apoB value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 52

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[66]	1488[67]		
Units: percent change				
arithmetic mean (standard deviation)				
Week 52 (n = 676, 1342)	3.4 (± 20.24)	-6.0 (± 22.54)		

Notes:
[66] - FAS
[67] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 24 in hsCRP

End point title	Percent Change From Baseline to Week 24 in 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 analyzed for hsCRP. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(hsCRP value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 24

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[68]	1488[69]		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Week 24 (n = 706, 1392)	2.727 (-33.028 to 59.016)	-16.382 (-51.329 to 34.436)		

Notes:

[68] - FAS

[69] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline to Week 52 in hsCRP

End point title	Percent Change From Baseline to Week 52 in 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 analyzed for hsCRP. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(hsCRP value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 52

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[70]	1488[71]		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Week 52 (n = 681, 1358)	1.818 (-36.508 to 60.952)	-14.445 (-50.000 to 43.889)		

Notes:

[70] - FAS

[71] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants Achieving LDL-C <70 mg/dL at Week 12, 24, and 52

End point title	Percentage of Participants Achieving LDL-C <70 mg/dL at Week 12, 24, and 52

End point description:

The percentage of participants who achieved lowering in lipid values of LDL-C below 70 mg/dL have been reported. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Observed data was used for the analysis, no imputation for the missing data was performed.

End point type	Other pre-specified

End point timeframe:

Week 12, Week 24, and Week 52

End point values	Placebo	Bempedoic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742[72]	1488[73]		
Units: Percentage of participants				
number (not applicable)				
Week 12, n = 725, 1424	9.0	32.4		
Week 24, n = 707, 1397	10.2	32.0		
Week 52, n = 685, 1364	9.5	28.2		

Notes:

[72] - FAS

[73] - FAS

Statistical analyses

Statistical analysis title	P value at Weeks 12, 24 and 52

Statistical analysis description:

P value of comparisons between treatment groups was calculated using Chi-square test.

Comparison groups	Placebo v Bempedoic acid
Number of subjects included in analysis	2230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 52 weeks

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Bempedoic Acid

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Bempedoic Acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	216 / 1487 (14.53%)	104 / 742 (14.02%)	
number of deaths (all causes)	13	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder cancer			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	3 / 1487 (0.20%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Lung squamous cell carcinoma metastatic			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal cancer			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	3 / 1487 (0.20%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
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 / 1487 (0.00%)	1 / 742 (0.13%)	
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	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure inadequately controlled			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
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	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 1487 (0.13%)	3 / 742 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eye complication associated with device			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granuloma			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pelvic mass			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	7 / 1487 (0.47%)	4 / 742 (0.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent restenosis			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 1487 (0.20%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 1487 (0.20%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic pneumonia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cyst			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit delirium			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (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			
Anaemia postoperative			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			

subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac function disturbance postoperative			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (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 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Myotonic dystrophy			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 1487 (0.00%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	11 / 1487 (0.74%)	5 / 742 (0.67%)	
occurrences causally related to treatment / all	0 / 13	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	11 / 1487 (0.74%)	6 / 742 (0.81%)	
occurrences causally related to treatment / all	0 / 15	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	18 / 1487 (1.21%)	12 / 742 (1.62%)	
occurrences causally related to treatment / all	0 / 19	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	7 / 1487 (0.47%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 1487 (0.07%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	5 / 1487 (0.34%)	3 / 742 (0.40%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 1487 (0.27%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	9 / 1487 (0.61%)	6 / 742 (0.81%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dilatation			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	4 / 1487 (0.27%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	8 / 1487 (0.54%)	5 / 742 (0.67%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (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			
Brain oedema			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery disease			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			

subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 1487 (0.20%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible ischaemic neurological deficit			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	3 / 1487 (0.20%)	3 / 742 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 1487 (0.20%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticular perforation			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal hernia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (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 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 1487 (0.20%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	3 / 1487 (0.20%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 1487 (0.07%)	2 / 742 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism primary			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Foot deformity			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 1487 (0.00%)	3 / 742 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (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	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 1487 (0.20%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	4 / 1487 (0.27%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter infection			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective aneurysm			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 1487 (0.40%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella bacteraemia			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 1487 (0.07%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal osteomyelitis			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 1487 (0.13%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis necroticans			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 1487 (0.13%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 1487 (0.00%)	1 / 742 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 1487 (0.07%)	0 / 742 (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	Bempedoic Acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	792 / 1487 (53.26%)	381 / 742 (51.35%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	35 / 1487 (2.35%)	13 / 742 (1.75%)	
occurrences (all)	36	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	42 / 1487 (2.82%)	26 / 742 (3.50%)	
occurrences (all)	44	27	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	24 / 1487 (1.61%)	19 / 742 (2.56%)	
occurrences (all)	27	22	
Nervous system disorders			

Dizziness			
subjects affected / exposed	65 / 1487 (4.37%)	31 / 742 (4.18%)	
occurrences (all)	69	33	
Headache			
subjects affected / exposed	45 / 1487 (3.03%)	24 / 742 (3.23%)	
occurrences (all)	61	27	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 1487 (2.76%)	15 / 742 (2.02%)	
occurrences (all)	43	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 1487 (2.56%)	25 / 742 (3.37%)	
occurrences (all)	38	26	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	43 / 1487 (2.89%)	19 / 742 (2.56%)	
occurrences (all)	48	22	
Constipation			
subjects affected / exposed	26 / 1487 (1.75%)	18 / 742 (2.43%)	
occurrences (all)	27	19	
Diarrhoea			
subjects affected / exposed	60 / 1487 (4.03%)	30 / 742 (4.04%)	
occurrences (all)	68	34	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	47 / 1487 (3.16%)	23 / 742 (3.10%)	
occurrences (all)	52	23	
Dyspnoea			
subjects affected / exposed	19 / 1487 (1.28%)	16 / 742 (2.16%)	
occurrences (all)	21	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	64 / 1487 (4.30%)	44 / 742 (5.93%)	
occurrences (all)	69	46	
Back pain			

subjects affected / exposed	55 / 1487 (3.70%)	18 / 742 (2.43%)	
occurrences (all)	58	19	
Muscle spasms			
subjects affected / exposed	62 / 1487 (4.17%)	20 / 742 (2.70%)	
occurrences (all)	72	22	
Myalgia			
subjects affected / exposed	89 / 1487 (5.99%)	45 / 742 (6.06%)	
occurrences (all)	102	53	
Osteoarthritis			
subjects affected / exposed	30 / 1487 (2.02%)	23 / 742 (3.10%)	
occurrences (all)	33	24	
Musculoskeletal pain			
subjects affected / exposed	40 / 1487 (2.69%)	19 / 742 (2.56%)	
occurrences (all)	45	22	
Pain in extremity			
subjects affected / exposed	50 / 1487 (3.36%)	16 / 742 (2.16%)	
occurrences (all)	56	17	
Infections and infestations			
Bronchitis			
subjects affected / exposed	52 / 1487 (3.50%)	19 / 742 (2.56%)	
occurrences (all)	55	24	
Lower respiratory tract infection			
subjects affected / exposed	41 / 1487 (2.76%)	19 / 742 (2.56%)	
occurrences (all)	45	19	
Sinusitis			
subjects affected / exposed	26 / 1487 (1.75%)	18 / 742 (2.43%)	
occurrences (all)	27	19	
Nasopharyngitis			
subjects affected / exposed	146 / 1487 (9.82%)	87 / 742 (11.73%)	
occurrences (all)	161	97	
Urinary tract infection			
subjects affected / exposed	70 / 1487 (4.71%)	47 / 742 (6.33%)	
occurrences (all)	81	60	
Upper respiratory tract infection			
subjects affected / exposed	72 / 1487 (4.84%)	31 / 742 (4.18%)	
occurrences (all)	83	37	

Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 32 / 1487 (2.15%) 66	 22 / 742 (2.96%) 36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2016	Protocol Amendment 1 dated 28 January 2016- Major changes to the protocol with this amendment included: • Addition of secondary and tertiary study objectives to evaluate lipid and cardiometabolic parameters at specific time points throughout the study • Addition of protocol requirements to address the recent marketing of proprotein convertase subtilisin kexin type 9i (PCSK9i) therapies resulting in the addition of exclusion criteria, prohibited medications instructions, and allowable medication instructions to reflect the protocol requirements • Defined clinical endpoints to provide clarity regarding the events that will be adjudicated by the clinical event committee • Revised the reporting requirements for clinical endpoints • Revised inclusion/exclusion criteria by aligning the medical history and concurrent conditions of the study population with those commonly observed in participants with hyperlipidemia and high cardiovascular risk • Revised safety monitoring and management instructions to ensure participant safety for the following: − elevated serum creatinine − hemoglobin − elevated creatine kinase − low-density lipoprotein cholesterol threshold criteria for the addition of adjunctive therapy beginning at Week 24 (Visit T5) − hypoglycemia
09 March 2016	Protocol Amendment 2 dated 23 February 2016- The major changes to the protocol with this amendment was for program consistency, revision of severity categories for adverse events to the 3 categories of severity.
09 September 2016	Protocol Amendment 3 dated 28 July 2016- Major changes to the protocol with this amendment included: • Increased sample size from 900 to 1950 randomized participants • Revised the high-dose statin exclusion to allow participants on high-dose statins with the exception of participants on simvastatin taking average daily doses that were greater than 40 mg. This revision was based upon the weak drug interactions observed with bempedoic acid 240 mg when given with low-dose statins. • Increased overall study duration to account for additional recruitment time required to randomize additional participants • Revised inclusion criteria to be consistent with current safety data and to comply with Health Canada requests − Revised to include tubal ligation in the study definition for “surgically sterile.” − Revised to include the birth control requirement as requested by Health Canada. This revision only applied to Canadian sites • Revised exclusion criteria to be consistent with current safety data. Revisions included: − Increased total fasting triglycerides, decreased the estimated glomerular filtration rate (eGFR), Allowed participants with positive hepatitis C-antibodies (HCV-AB) results to have a reflex HCV RNA performed so that those participants without active disease may have been considered for enrolment, allowed participants whose total bilirubin levels exceeded ≥1.2 × Upper limit normal to have a reflex indirect (unconjugated) bilirubin test so that those participants with results that were consistent with Gilbert’s disease, shortened the duration from when a participant may have had, for any reason, a blood transfusion, decreased the amount of time participants should be stable on obesity medications, removed the collection of blood samples for pharmacokinetic assessment for those participants who were randomized into the study after the implementation of Protocol Amendment 3.

06 December 2016	Protocol Amendment 4 dated 14 October 2016- Major changes to the protocol with this amendment included: • Revised exclusion criteria to be consistent with current safety data and to comply with US Food and Drug Administration (FDA) request. Excluded renally impaired participants receiving an average daily dose of simvastatin 40 mg with eGFR <45 milliliter per minute per 1.73 square meter (mL/min/1.73^m2). • To comply with US FDA request, additional visits (2 in the clinic and 2 by telephone) were added for clinical safety laboratory evaluations and adverse event monitoring for participants receiving an average daily dose of simvastatin 40 mg
03 July 2017	Protocol Amendment 5 dated 10 May 2017- Major changes to the protocol with this amendment included: • Simvastatin at average daily doses of 40 mg or greater was added as a prohibited medication. • Revised the collection of reserve samples to allow Sponsor to discontinue collection after a sufficient number of samples were collected • Revised procedures for Visits T4.1, T4.2, T5.1, and T5.2 to indicate that participants who were discontinued from study drug because they were on simvastatin 40 mg or greater and who provided consent to be followed in the safety follow-up should be scheduled for these visits • Added a procedure to Visit T7 for participants who completed the study while taking study drug to collect information regarding whether: 1) the participant was offered the open-label extension study (Study 1002-050) and 2) if not, the reason that the open-label extension study was not offered to the participant • To further ensure participant safety, the monitoring and management of creatine kinase (CK) was revised to include additional instructions for the investigator in cases where the repeat CK was confirmed to be greater than 5 × upper limit of normal (ULN) and the participant was asymptomatic.

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/30865796