



Clinical trial results: A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg Summary

EudraCT number	2016-004115-12
Trial protocol	DE NL PL GB
Global end of trial date	05 November 2019

Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021

Trial information

Trial identification

Sponsor protocol code	1002-050
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03067441
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Esperion Therapeutics, Inc.
Sponsor organisation address	3891 Ranchero Drive, Suite 150, Ann Arbor, Michigan, United States, 48108
Public contact	Esperion Therapeutics, Inc., Esperion Therapeutics, Inc., +1 833 377 7633, medinfo@esperion.com
Scientific contact	Esperion Therapeutics, Inc., Esperion Therapeutics, Inc., +1 833 377 7633, medinfo@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	06 December 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 milligrams (mg).

Protection of trial subjects:

This study was designed, conducted, and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy:

Enrolled subjects received stable background lipid-modifying therapy(ies), including a maximally tolerated statin, throughout the study.

Evidence for comparator: -

Actual start date of recruitment	03 February 2017
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	United States: 362
Country: Number of subjects enrolled	Canada: 174
Country: Number of subjects enrolled	Netherlands: 108
Country: Number of subjects enrolled	Poland: 395
Country: Number of subjects enrolled	United Kingdom: 145
Country: Number of subjects enrolled	Germany: 278
Worldwide total number of subjects	1462
EEA total number of subjects	926

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)	519
From 65 to 84 years	927
85 years and over	16

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After successfully completing 52 weeks of treatment in the parent study, Study 1002-040 (NCT02666664), and meeting entry criteria, participants could enroll into this Open-label Extension (OLE) study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo; Bempedoic Acid

Arm description:

In the parent study (Study 1002-040), 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. Participants received open-label bempedoic acid 180 milligrams (mg) once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of investigational medicinal product (IMP).

Arm type	Experimental
Investigational medicinal product name	Bempedoic acid
Investigational medicinal product code	ETC-1002
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

180 mg film-coated tablets, administered daily with or without food

Arm title	Bempedoic Acid; Bempedoic Acid
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Arm description:

In the parent study, 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. Participants received open-label bempedoic acid 180 mg once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of IMP.

Arm type	Experimental
Investigational medicinal product name	Bempedoic acid
Investigational medicinal product code	ETC-1002
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

180 mg film-coated tablets, administered daily with or without food

Number of subjects in period 1	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid
Started	492	970
Completed	459	913
Not completed	33	57
Consent withdrawn by subject	16	34
Physician decision	1	3
Adverse event, non-fatal	7	14
Study Terminated by Sponsor or Investigator	1	-
Unknown	1	1
Lost to follow-up	7	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo; Bempedoic Acid
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Reporting group description:

In the parent study (Study 1002-040), 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. Participants received open-label bempedoic acid 180 milligrams (mg) once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of investigational medicinal product (IMP).

Reporting group title	Bempedoic Acid; Bempedoic Acid
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Reporting group description:

In the parent study, 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. Participants received open-label bempedoic acid 180 mg once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of IMP.

Reporting group values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	Total
Number of subjects	492	970	1462
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	67.5	66.5	
standard deviation	± 8.54	± 8.81	-

Gender categorical

Data for the OLE Bempedoic Acid arm are reported in the "Total" column.

Units: Subjects			
Female	142	239	381
Male	350	731	1081

Race (NIH/OMB)

Data for the OLE Bempedoic Acid arm are reported in the "Total" column.

Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	5	9	14
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	6	23	29
White	480	931	1411
More Than One Race	0	1	1
Unknown or Not Reported	1	3	4

Low-density lipoprotein cholesterol (LDL-C): Parent Study

Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).

Units: milligrams per deciliter (mg/dL)			
arithmetic mean	98.96	102.94	
standard deviation	± 24.171	± 29.899	-

Non-high-density lipoprotein cholesterol (NHDLC): Parent Study

Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).

Units: mg/dL			
arithmetic mean	126.41	130.09	
standard deviation	± 28.531	± 34.727	-
Total cholesterol: Parent Study			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
arithmetic mean	175.33	178.94	
standard deviation	± 30.026	± 36.057	-
Apolipoprotein B: Parent Study			
Baseline was defined as the last value prior to first dose of study drug. Only subjects with non-missing data were analysed. N = 487 for Placebo; Bempedoic Acid. N = 969 for Bempedoic Acid; Bempedoic Acid. N = 1456 for OLE Bempedoic Acid.			
Units: mg/dL			
arithmetic mean	85.1	88.2	
standard deviation	± 19.25	± 21.71	-
High-sensitivity C-reactive protein (hs-CRP): Parent Study			
Baseline was defined as the last value prior to the first dose of study drug. Only participants with non-missing data were analysed. N = 490 for Placebo; Bempedoic Acid. N = 969 for Bempedoic Acid; Bempedoic Acid. N = 1459 for OLE Bempedoic Acid.			
Units: milligrams per Liter (mg/L)			
median	1.515	1.500	
inter-quartile range (Q1-Q3)	0.810 to 3.490	0.700 to 3.220	-
Triglycerides: Parent Study			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
median	122.00	125.00	
inter-quartile range (Q1-Q3)	97.50 to 169.25	97.00 to 164.50	-
High-density lipoprotein cholesterol (HDL-C): Parent Study			
Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1).			
Units: mg/dL			
arithmetic mean	48.93	48.82	
standard deviation	± 11.206	± 11.790	-
LDL-C: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/dL			
arithmetic mean	99.5	86.6	
standard deviation	± 28.59	± 30.18	-
N-HDL-C: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/dL			
arithmetic mean	126.1	113.7	
standard deviation	± 32.61	± 34.57	-
Total cholesterol: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/dL			
arithmetic mean	175.2	159.8	
standard deviation	± 34.23	± 36.41	-
Apolipoprotein B: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/dL			
arithmetic mean	87.6	80.4	
standard deviation	± 22.74	± 21.31	-

hs-CRP: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/L			
median	1.560	1.250	
inter-quartile range (Q1-Q3)	0.745 to 3.015	0.620 to 2.480	-
Triglycerides: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/dL			
median	120.00	121.0	
inter-quartile range (Q1-Q3)	91.5 to 165.0	88.0 to 172.0	-
HDL-C: OLE Study			
Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.			
Units: mg/dL			
arithmetic mean	49.0	46.1	
standard deviation	± 11.72	± 13.00	-

End points

End points reporting groups

Reporting group title	Placebo; Bempedoic Acid
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Reporting group description:

In the parent study (Study 1002-040), 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. Participants received open-label bempedoic acid 180 milligrams (mg) once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of investigational medicinal product (IMP).

Reporting group title	Bempedoic Acid; Bempedoic Acid
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Reporting group description:

In the parent study, 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. Participants received open-label bempedoic acid 180 mg once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of IMP.

Subject analysis set title	OLE Bempedoic Acid
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Subject analysis set type	Full analysis
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Subject analysis set description:

In the parent study, participants received either bempedoic acid 180 mg tablet or matching placebo, 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. Participants received open-label bempedoic acid 180 mg once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of IMP.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) ^[1]
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End point description:

TEAEs are defined as adverse events that began or worsened in severity after the first dose of investigational medicinal product (IMP) until 30 days after the last dose in the Open-Label Extension (OLE) Study.

End point type	Primary
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End point timeframe:

Up to Week 82

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: No statistical analysis was conducted.

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[2]	970 ^[3]	1462 ^[4]	
Units: subjects				
Subjects with TEAEs	385	758	1143	
Subjects with serious TEAEs	97	202	299	
Subjects with TEAEs of mild severity	93	195	288	
Subjects with TEAEs of moderate severity	211	403	614	
Subjects with TEAEs of severe severity	81	160	241	

Notes:

[2] - Safety Population: enrolled subjects who received at least 1 dose of bempedoic acid in the OLE Study

[3] - Safety Population

[4] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in Low-Density Lipoprotein Cholesterol (LDL-C) at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in Low-Density Lipoprotein Cholesterol (LDL-C) at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: LDL-C value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[5]	970 ^[6]	1462 ^[7]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=464, 909, 1373	-12.82 (± 23.419)	-13.80 (± 25.018)	-13.47 (± 24.485)	
Week 78, n=433, 865, 1298	-14.99 (± 23.660)	-14.15 (± 25.113)	-14.43 (± 24.632)	

Notes:

[5] - Safety Population. Only subjects with available data were analyzed.

[6] - Safety Population. Only subjects with available data were analyzed.

[7] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Parent Study Baseline in LDL-C at Weeks 52 and 78

End point title	Mean Change From Parent Study Baseline in LDL-C at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Mean change from Baseline was calculated as: Mean LDL-C value at Week 52/Week 78 minus Mean Parent Study Baseline value. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
End point timeframe:	
Baseline; Week 52 and Week 78	

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[8]	970 ^[9]	1462 ^[10]	
Units: milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Week 52, n=464, 909, 1373	-14.08 (± 24.995)	-15.77 (± 28.123)	-15.19 (± 27.109)	
Week 78, n=433, 865, 1298	-16.11 (± 25.628)	-16.04 (± 28.929)	-16.06 (± 27.862)	

Notes:

[8] - Safety Population. Only subjects with available data were analyzed.

[9] - Safety Population. Only subjects with available data were analyzed.

[10] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: non-HDL-C value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
End point timeframe:	
Baseline; Week 52 and Week 72	

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[11]	970 ^[12]	1462 ^[13]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=463, 909, 1372	-10.60 (± 20.722)	-10.55 (± 22.682)	-10.57 (± 22.033)	
Week 78, n=433, 865, 1298	-12.50 (± 22.081)	-10.82 (± 23.910)	-11.38 (± 23.321)	

Notes:

[11] - Safety Population. Only subjects with available data were analyzed.

[12] - Safety Population. Only subjects with available data were analyzed.

[13] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in Total Cholesterol at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in Total Cholesterol at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: Total cholesterol value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[14]	970 ^[15]	1462 ^[16]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=464, 910, 1374	-9.01 (± 15.961)	-9.79 (± 16.893)	-9.53 (± 16.582)	
Week 78, n=433, 865, 1298	-10.15 (± 16.541)	-9.34 (± 18.030)	-9.61 (± 17.545)	

Notes:

[14] - Safety Population. Only subjects with available data were analyzed.

[15] - Safety Population. Only subjects with available data were analyzed.

[16] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in Apolipoprotein B (ApoB) at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in Apolipoprotein B (ApoB) at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: ApoB value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
End point timeframe:	
Baseline; Week 52 and Week 78	

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[17]	970 ^[18]	1462 ^[19]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=458, 905, 1363	-7.5 (± 20.52)	-8.8 (± 21.89)	-8.4 (± 21.44)	
Week 78, n=424, 858, 1282	-7.6 (± 22.15)	-7.0 (± 22.33)	-7.2 (± 22.26)	

Notes:

[17] - Safety Population. Only subjects with available data were analyzed.

[18] - Safety Population. Only subjects with available data were analyzed.

[19] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in High-Sensitivity C-Reactive Protein (Hs-CRP) at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in High-Sensitivity C-Reactive Protein (Hs-CRP) at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: hs-CRP value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
End point timeframe:	
Baseline; Week 52 and Week 78	

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[20]	970 ^[21]	1462 ^[22]	
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Week 52, n=462, 908, 1370	-11.553 (-53.120 to 44.167)	-19.709 (-52.617 to 34.151)	-16.476 (-52.874 to 41.667)	
Week 78, n=431, 865, 1296	-15.005 (-50.510 to 44.000)	-18.065 (-51.701 to 50.505)	-16.740 (-51.577 to 48.279)	

Notes:

[20] - Safety Population. Only subjects with available data were analyzed.

[21] - Safety Population. Only subjects with available data were analyzed.

[22] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in Triglycerides at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in Triglycerides at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: Triglycerides value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[23]	970 ^[24]	1462 ^[25]	
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Week 52, n=464, 909, 1373	-4.31 (-24.08 to 21.75)	-3.21 (-22.76 to 23.50)	-3.49 (-23.02 to 22.40)	
Week 78, n=433, 865, 1298	-5.00 (-25.54 to 24.26)	-2.60 (-21.41 to 27.47)	-3.08 (-22.78 to 26.67)	

Notes:

[23] - Safety Population. Only subjects with available data were analyzed.

[24] - Safety Population. Only subjects with available data were analyzed.

[25] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Parent Study Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 52 and 78

End point title	Percent Change From Parent Study Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: HDL-C value at Week 52/Week 78 minus Parent Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1) in the Parent Study.

End point type	Secondary
End point timeframe:	
Baseline; Week 52 and Week 78	

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[26]	970 ^[27]	1462 ^[28]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=464, 907, 1371	-4.54 (± 16.747)	-7.06 (± 15.638)	-6.20 (± 16.060)	
Week 78, n=433, 863, 1296	-3.42 (± 17.555)	-4.91 (± 16.731)	-4.41 (± 17.018)	

Notes:

[26] - Safety Population. Only subjects with available data were analyzed.

[27] - Safety Population. Only subjects with available data were analyzed.

[28] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Open-Label Extension (OLE) Study Baseline in LDL-C at Weeks 52 and 78

End point title	Percent Change From Open-Label Extension (OLE) Study Baseline in LDL-C at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: LDL-C value at Week 52/Week 78 minus OLE Study Baseline value divided by Parent Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
End point timeframe:	
Baseline; Week 52 and Week 78	

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[29]	970 ^[30]	1462 ^[31]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=464, 909, 1373	-12.4 (± 23.79)	3.6 (± 27.49)	-1.8 (± 27.35)	
Week 78, n=433, 865, 1298	-14.3 (± 25.79)	3.7 (± 30.63)	-2.3 (± 30.31)	

Notes:

[29] - Safety Population. Only subjects with available data were analyzed.

[30] - Safety Population. Only subjects with available data were analyzed.

[31] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From OLE Baseline in LDL-C at Weeks 52 and 78

End point title	Mean Change From OLE Baseline in LDL-C at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Mean change from Baseline was calculated as: Mean LDL-C value at Week 52/Week 78 minus Mean OLE Study Baseline value. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 72

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[32]	970 ^[33]	1462 ^[34]	
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 52, n=464, 909, 1373	-14.7 (± 25.63)	0.6 (± 24.92)	-4.6 (± 26.17)	
Week 78, n=433, 865, 1298	-17.0 (± 28.56)	0.2 (± 26.04)	-5.5 (± 28.08)	

Notes:

[32] - Safety Population. Only subjects with available data were analyzed.

[33] - Safety Population. Only subjects with available data were analyzed.

[34] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From OLE Baseline in Non-HDL-C at Weeks 52 and 78

End point title	Percent Change From OLE Baseline in Non-HDL-C at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: non-HDL-C value at Week 52/Week 78 minus OLE Study Baseline value divided by OLE Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[35]	970 ^[36]	1462 ^[37]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=463, 909, 1372	-10.0 (± 20.81)	2.9 (± 23.98)	-1.4 (± 23.75)	
Week 78, n=433, 865, 1298	-11.8 (± 23.08)	3.1 (± 28.02)	-1.9 (± 27.38)	

Notes:

[35] - Safety Population. Only subjects with available data were analyzed.

[36] - Safety Population. Only subjects with available data were analyzed.

[37] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From OLE Baseline in Total Cholesterol at Weeks 52 and 78

End point title	Percent Change From OLE Baseline in Total Cholesterol at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: Total Cholesterol value at Week 52/Week 78 minus OLE Study Baseline value divided by OLE Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[38]	970 ^[39]	1462 ^[40]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=464, 910, 1374	-8.7 (± 15.78)	1.3 (± 17.23)	-2.1 (± 17.40)	
Week 78, n=433, 865, 1298	-9.7 (± 17.39)	2.1 (± 19.88)	-1.8 (± 19.88)	

Notes:

[38] - Safety Population. Only subjects with available data were analyzed.

[39] - Safety Population. Only subjects with available data were analyzed.

[40] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From OLE Baseline ApoB at Weeks 52 and 78

End point title	Percent Change From OLE Baseline ApoB at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: ApoB value at Week 52/Week 78 minus OLE Study Baseline value divided by OLE Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[41]	970 ^[42]	1462 ^[43]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=463, 906, 1369	-10.0 (± 19.94)	0.2 (± 21.48)	-3.2 (± 21.51)	
Week 78, n=428, 858, 1286	-10.2 (± 21.84)	2.4 (± 23.16)	-1.8 (± 23.49)	

Notes:

[41] - Safety Population. Only subjects with available data were analyzed.

[42] - Safety Population. Only subjects with available data were analyzed.

[43] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From OLE Baseline in Hs-CRP at Weeks 52 and 78

End point title	Percent Change From OLE Baseline in Hs-CRP at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: hs-CRP value at Week 52/Week 78 minus OLE Study Baseline value divided by OLE Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[44]	970 ^[45]	1462 ^[46]	
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Week 52, n=464, 909, 1373	-11.720 (- 50.315 to 38.433)	-2.174 (- 39.583 to 61.765)	-4.856 (- 43.750 to 52.800)	
Week 78, n=433, 865, 1298	-14.953 (- 50.549 to 43.333)	3.774 (-36.842 to 69.136)	-2.538 (- 41.509 to 60.268)	

Notes:

[44] - Safety Population. Only subjects with available data were analyzed.

[45] - Safety Population. Only subjects with available data were analyzed.

[46] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From OLE Baseline in Triglycerides at Weeks 52 and 78

End point title	Percent Change From OLE Baseline in Triglycerides at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: Triglycerides value at Week 52/Week 78 minus OLE Study Baseline value divided by OLE Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[47]	970 ^[48]	1373 ^[49]	
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Week 52, n=464, 909, 1373	0.3 (-22.4 to 23.6)	0.9 (-20.2 to 25.2)	0.7 (-20.7 to 24.3)	
Week 78, n=433, 865, 1298	-2.0 (-23.8 to 24.1)	2.2 (-19.2 to 27.2)	0.9 (-20.9 to 26.6)	

Notes:

[47] - Safety Population. Only subjects with available data were analyzed.

[48] - Safety Population. Only subjects with available data were analyzed.

[49] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From OLE Baseline in HDL-C at Weeks 52 and 78

End point title	Percent Change From OLE Baseline in HDL-C at Weeks 52 and 78
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End point description:

Blood samples were drawn after a minimum 10-hour fast at pre-specified intervals. Percent change from Baseline was calculated as: HDL-C value at Week 52/Week 78 minus OLE Study Baseline value divided by OLE Study Baseline value multiplied by 100. Baseline was defined as the last non-missing record prior to treatment start in the OLE Study.

End point type	Secondary
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End point timeframe:

Baseline; Week 52 and Week 78

End point values	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	492 ^[50]	970 ^[51]	1462 ^[52]	
Units: percent change				
arithmetic mean (standard deviation)				
Week 52, n=464, 907, 1371	-4.3 (± 18.36)	-0.6 (± 14.88)	-1.8 (± 16.23)	
Week 78, n=433, 863, 1296	-3.4 (± 17.77)	2.7 (± 23.60)	0.7 (± 22.01)	

Notes:

[50] - Safety Population. Only subjects with available data were analyzed.

[51] - Safety Population. Only subjects with available data were analyzed.

[52] - Safety Population. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 82

Adverse event reporting additional description:

Treatment-emergent adverse events, defined as adverse events that began or worsened in severity after the first dose of investigational medicinal product (IMP) until 30 days after the last dose in the Open-Label Extension (OLE) study, are reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo; Bempedoic Acid
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Reporting group description:

In the parent study (Study 1002-040), 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. Participants received open-label bempedoic acid 180 milligrams (mg) once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of investigational medicinal product (IMP).

Reporting group title	Bempedoic Acid; Bempedoic Acid
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Reporting group description:

In the parent study, 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. Participants received open-label bempedoic acid 180 mg once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of IMP.

Reporting group title	OLE Bempedoic Acid
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Reporting group description:

In the parent study, participants received either bempedoic acid 180 mg tablet or matching placebo, 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. Participants received open-label bempedoic acid 180 mg once daily by mouth for up to 78 weeks after rolling over from the parent study, followed by a 4-week period off of IMP.

Serious adverse events	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 492 (19.72%)	202 / 970 (20.82%)	299 / 1462 (20.45%)
number of deaths (all causes)	3	10	13
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	2 / 492 (0.41%)	2 / 970 (0.21%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Adenocarcinoma of colon			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	2 / 492 (0.41%)	0 / 970 (0.00%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Adenocarcinoma			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear cell renal cell carcinoma			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypergammaglobulinaemia benign monoclonal			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage III			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage IV			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Papillary renal cell carcinoma			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extranodal marginal zone B-cell lymphoma (MALT type)			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal neoplasm			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 492 (0.61%)	5 / 970 (0.52%)	8 / 1462 (0.55%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	4 / 492 (0.81%)	0 / 970 (0.00%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	1 / 492 (0.20%)	2 / 970 (0.21%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery aneurysm			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiodysplasia			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 492 (0.20%)	8 / 970 (0.82%)	9 / 1462 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 8	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 492 (0.20%)	4 / 970 (0.41%)	5 / 1462 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Accidental death			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Brain death			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Hernia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent occlusion			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 492 (0.00%)	4 / 970 (0.41%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 492 (0.20%)	3 / 970 (0.31%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 492 (0.41%)	0 / 970 (0.00%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure decreased			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress echocardiogram abnormal			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ultrasound ovary abnormal			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Femoral neck fracture			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal anastomosis complication			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft occlusion			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprocedural myocardial infarction			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Multiple endocrine neoplasia Type 1			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	3 / 492 (0.61%)	15 / 970 (1.55%)	18 / 1462 (1.23%)
occurrences causally related to treatment / all	0 / 4	0 / 16	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 492 (0.41%)	12 / 970 (1.24%)	14 / 1462 (0.96%)
occurrences causally related to treatment / all	0 / 2	1 / 14	1 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina pectoris			
subjects affected / exposed	5 / 492 (1.02%)	9 / 970 (0.93%)	14 / 1462 (0.96%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	3 / 492 (0.61%)	10 / 970 (1.03%)	13 / 1462 (0.89%)
occurrences causally related to treatment / all	0 / 3	1 / 12	1 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 492 (0.41%)	7 / 970 (0.72%)	9 / 1462 (0.62%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	3 / 492 (0.61%)	6 / 970 (0.62%)	9 / 1462 (0.62%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Myocardial infarction			
subjects affected / exposed	2 / 492 (0.41%)	6 / 970 (0.62%)	8 / 1462 (0.55%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 492 (0.00%)	5 / 970 (0.52%)	5 / 1462 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	3 / 492 (0.61%)	2 / 970 (0.21%)	5 / 1462 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 492 (0.00%)	4 / 970 (0.41%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			

subjects affected / exposed	0 / 492 (0.00%)	3 / 970 (0.31%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	2 / 492 (0.41%)	0 / 970 (0.00%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anginal equivalent			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachyarrhythmia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	2 / 492 (0.41%)	6 / 970 (0.62%)	8 / 1462 (0.55%)
occurrences causally related to treatment / all	0 / 2	0 / 9	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 492 (0.41%)	3 / 970 (0.31%)	5 / 1462 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 492 (0.20%)	3 / 970 (0.31%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 492 (0.20%)	2 / 970 (0.21%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery occlusion			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
External compression headache			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Intracranial aneurysm			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 492 (0.41%)	1 / 970 (0.10%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal lymphadenopathy			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haematoma			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 492 (0.20%)	6 / 970 (0.62%)	7 / 1462 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	4 / 492 (0.81%)	1 / 970 (0.10%)	5 / 1462 (0.34%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	2 / 492 (0.41%)	1 / 970 (0.10%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal ulcer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 492 (0.20%)	3 / 970 (0.31%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 492 (0.20%)	2 / 970 (0.21%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis contact			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 492 (0.41%)	6 / 970 (0.62%)	8 / 1462 (0.55%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	3 / 492 (0.61%)	2 / 970 (0.21%)	5 / 1462 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition disorder			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal cyst			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperparathyroidism primary			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Osteoarthritis			
subjects affected / exposed	4 / 492 (0.81%)	6 / 970 (0.62%)	10 / 1462 (0.68%)
occurrences causally related to treatment / all	0 / 5	0 / 8	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 492 (0.20%)	3 / 970 (0.31%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	2 / 492 (0.41%)	2 / 970 (0.21%)	4 / 1462 (0.27%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 492 (0.20%)	1 / 970 (0.10%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 492 (0.41%)	0 / 970 (0.00%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compartment syndrome			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 492 (1.22%)	9 / 970 (0.93%)	15 / 1462 (1.03%)
occurrences causally related to treatment / all	0 / 6	0 / 9	0 / 15
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	2 / 492 (0.41%)	4 / 970 (0.41%)	6 / 1462 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 492 (0.00%)	2 / 970 (0.21%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 492 (0.41%)	0 / 970 (0.00%)	2 / 1462 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			

subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node tuberculosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 492 (0.41%)	1 / 970 (0.10%)	3 / 1462 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 492 (0.00%)	1 / 970 (0.10%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			

subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 492 (0.20%)	0 / 970 (0.00%)	1 / 1462 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo; Bempedoic Acid	Bempedoic Acid; Bempedoic Acid	OLE Bempedoic Acid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 492 (21.95%)	201 / 970 (20.72%)	309 / 1462 (21.14%)
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 492 (6.10%)	38 / 970 (3.92%)	68 / 1462 (4.65%)
occurrences (all)	38	40	78
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 492 (6.71%)	86 / 970 (8.87%)	119 / 1462 (8.14%)
occurrences (all)	39	100	139
Upper respiratory tract infection			
subjects affected / exposed	18 / 492 (3.66%)	49 / 970 (5.05%)	67 / 1462 (4.58%)
occurrences (all)	21	54	75
Urinary tract infection			
subjects affected / exposed	40 / 492 (8.13%)	49 / 970 (5.05%)	89 / 1462 (6.09%)
occurrences (all)	54	52	106

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2017	<ul style="list-style-type: none">• Updated the design schematic to represent subjects could receive ETC-1002 or matching placebo in the parent study• Revised inclusion criteria to specify the requirements pertaining to the parent study• Updated exclusion criteria with regards to contraception to be consistent with European Medicines Agency (EMA) requirements• Based upon the recommendation of the Data Monitoring Committee and Esperion's decision, doses of simvastatin 40 milligrams (mg)/day or greater were added as a prohibited medication.• The instructions around maintaining study blind were expanded.• Procedures were clarified for subjects enrolling into the study after the last visit for the parent study.• The monitoring and management of creatine kinase (CK) values for asymptomatic subjects was modified to be consistent with other protocols across the program.• The Schedule of Events was updated to reflect changes or correct errors.• Typographical errors and formatting were corrected or revised based on these changes or to improve clarity and consistency.
15 January 2018	<ul style="list-style-type: none">• Updated contact details for Sponsor Contact and Medical Monitor• Revised the study design to include an assessment at Week 82, 4 weeks after subjects completed their last dose of bempedoic acid. This assessment was added to have safety and efficacy data off study drug to help interpret any potential findings during the treatment period.• Updated the design schematic to include the 4-week follow-up period from Week 78 to Week 82• Week 78 was called the End of Treatment (EOT) visit and Week 82 was described as the Off Study Drug Period/End of Study (EOS) visit.• The section on Background of Bempedoic Acid was updated to reflect the current version of the Investigator's Brochure.• The section on Concomitant Medications was revised to avoid changes in lipid-lowering medications during the 4-week washout period to limit the introduction of medications that may affect endpoints of interest measured at Week 82.• The statistical analysis plan for renal events was updated to remove text that indicated muscle-related events would be analyzed based on Baseline estimated glomerular filtration rate (eGFR). There was no data or clinical justification to justify assessment of muscle-related events by eGFR.• Text throughout the protocol was updated to reflect the addition of the 4-week follow-up period.• Typographical errors and formatting were corrected or revised based on these changes or to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported