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

## Summary

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

**Results information**

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

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1002-047 |

**Additional study identifiers**

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

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 25 September 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 September 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 18 November 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 237 |
| Country: Number of subjects enrolled | United Kingdom: 119 |
| Country: Number of subjects enrolled | Germany: 78 |

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

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 379 |
| From 65 to 84 years | 395 |
| 85 years and over | 5 |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

The study consisted of 3 periods: a 1-week screening period; a 4-week single-blind, placebo run-in period; and a 52-week double-blind, randomized treatment period.

### Period 1

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

Blinding implementation details:

The Sponsor, all clinical site personnel (e.g., investigator, pharmacist), and other vendor personnel were blinded to the treatment group for each participant. Participants were also blinded to the treatment they received. Blinding of treatment was required to be maintained for all participants unless, in the opinion of the investigator, the safety of the participant might be at risk.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

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

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

Dosage and administration details:

Participants received a placebo tablet once daily by mouth for 52 weeks during the double-blind treatment period.

| | |
|---|---|
| **Arm title** | Bempedoic acid |

Arm description:

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

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | bempedoic acid |
| Investigational medicinal product code | ETC-1002 |
| Other name | - |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

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

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

## Baseline characteristics

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

| Reporting group values | Placebo | Bempedoic acid | Total |
|---|---|---|---|
| Number of subjects | 257 | 522 | 779 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 64.7 | 64.1 | |
| standard deviation | ± 8.73 | ± 8.82 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 89 | 194 | 283 |
| Male | 168 | 328 | 496 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 0 | 4 | 4 |
| Black or African American | 12 | 24 | 36 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| White | 244 | 491 | 735 |
| Multiple | 0 | 2 | 2 |
| Mean low-density lipoprotein cholesterol (LDL-C) | | | |
| Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. | | | |
| Units: milligrams per deciliter (mg/dL) | | | |
| arithmetic mean | 122.4 | 119.4 | |
| standard deviation | ± 38.30 | ± 37.75 | - |
| Mean non-high-density lipoprotein cholesterol (non-HDL-C) | | | |
| Baseline was defined as the mean of the non-HDL-C values from the last two non-missing values on or prior to Day 1. | | | |
| Units: mg/dL | | | |
| arithmetic mean | 153.7 | 150.7 | |
| standard deviation | ± 44.36 | ± 42.75 | - |

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

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

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

| Reporting group title | Bempedoic acid |
|---|---|

Reporting group description:

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

### Primary: Percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C)

| End point title | Percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C) |
|---|---|

End point description:

Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline; Week 12

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

Notes:

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

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

### Statistical analyses

| Statistical analysis title | Difference [bempedoic acid - placebo] in LS mean |
|---|---|

Statistical analysis description:

The analysis compared treatment groups using a two-sided test at the 0.05 level of significance and a confidence interval (CI) of 95%. Data were analyzed using analysis of covariance (ANCOVA), with treatment group and randomization stratification factors (cardiovascular risk and Baseline statin intensity) as factors and Baseline LDL-C as a covariate.

| Comparison groups | Bempedoic acid v Placebo |
|---|---|

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

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

| | |
|---|---|
| End point title | Percent change from baseline to Week 24 in LDL-C |

End point description:

Baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline; Week 24

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

Notes:

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

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

### Statistical analyses

| **Statistical analysis title** | Difference [bempedoic acid - placebo] in LS mean |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Placebo v Bempedoic acid |

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

## Secondary: Percent change from baseline to Week 12 in non-high-density lipoprotein cholesterol (non-HDL-C)

| | |
|---|---|
| End point title | Percent change from baseline to Week 12 in non-high-density lipoprotein cholesterol (non-HDL-C) |

End point description:

Baseline was defined as the mean of the non-HDL-C values from the last two non-missing values on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline; Week 12

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

Notes:

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

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

## Statistical analyses

| **Statistical analysis title** | Difference [bempedoic acid - placebo] in LS mean |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Placebo v Bempedoic acid |

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

## Secondary: Percent change from baseline to Week 12 in total cholesterol (TC)

| | |
|---|---|
| End point title | Percent change from baseline to Week 12 in total cholesterol (TC) |

End point description:

Baseline was defined as the mean of the TC values from the last two non-missing values on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline; Week 12

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

Notes:

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

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

### Statistical analyses

| **Statistical analysis title** | Difference [bempedoic acid - placebo] in LS mean |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Placebo v Bempedoic acid |

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

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

| | |
|---|---|
| End point title | Percent change from baseline to Week 12 in apolipoprotein b (apo B) |

End point description:

Baseline for apo B was defined as the last non-missing value on or prior to Day 1. Percent change from Baseline is calculated as ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. The Full Analysis Set was comprised of all randomized participants.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline; Week 12

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

Notes:

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

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

### Statistical analyses

| **Statistical analysis title** | Difference [bempedoic acid - placebo] in LS mean |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Placebo v Bempedoic acid |

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

## Secondary: Percent change from baseline to Week 12 in high-sensitivity c-reactive protein (hsCRP)

| | |
|---|---|
| End point title | Percent change from baseline to Week 12 in high-sensitivity c-reactive protein (hsCRP) |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline; Week 12

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

Notes:

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

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

## Statistical analyses

| Statistical analysis title | Wilcoxon Two Sample Test |
|---|---|

Statistical analysis description:

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

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

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

| | |
|---|---|
| End point title | Change from baseline to Week 12 in LDL-C |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline; Week 12

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

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Change from baseline to Week 24 in LDL-C |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Baseline; Week 24

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to Week 52

Adverse event reporting additional description:

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

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Bempedoic acid |

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 522 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Bempedoic acid | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 88 / 257 (34.24%) | 211 / 522 (40.42%) | |
| Investigations | | | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 14 / 522 (2.68%) | |
| occurrences (all) | 1 | 14 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 257 (2.33%) | 7 / 522 (1.34%) | |
| occurrences (all) | 6 | 7 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 9 / 257 (3.50%) | 8 / 522 (1.53%) | |
| occurrences (all) | 9 | 10 | |
| Headache | | | |
| subjects affected / exposed | 7 / 257 (2.72%) | 10 / 522 (1.92%) | |
| occurrences (all) | 7 | 12 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 257 (1.17%) | 14 / 522 (2.68%) | |
| occurrences (all) | 3 | 15 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 257 (3.50%) | 6 / 522 (1.15%) | |
| occurrences (all) | 10 | 6 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 257 (2.72%) | 16 / 522 (3.07%) | |
| occurrences (all) | 8 | 18 | |
| Musculoskeletal and connective tissue | | | |

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported