



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 1002-040 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02666664 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Esperion Therapeutics Inc.  |
| Sponsor organisation address | Bldg. I: 3891 Ranchero Drive, Suite 150, Ann Arbor, United States, 48108                            |
| Public contact               | Director of Clinical Operations, Esperion Therapeutics, 001 7348873903, clinicaltrials@esperion.com |
| Scientific contact           | Director of Clinical Operations, Esperion Therapeutics, 001 7348873903, clinicaltrials@esperion.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 28 March 2018    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 February 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary purpose of the study was to evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk participants with hyperlipidemia [with underlying heterozygous familial hypercholesterolemia (HeFH) and/or atherosclerotic cardiovascular diseases (ASCVD)] who were not adequately controlled with their maximally tolerated lipid-modifying therapy, including maximally tolerated statin therapy.

Protection of trial subjects:

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

Background therapy:

Participants were required to be on stable lipid-modifying therapy (ies), including a maximally tolerated statin for at least 4 weeks prior to screening. Use of fibrates must have been stable at least 6 weeks prior to screening. Stable lipid-modifying therapy(s) included, but was not limited to, monotherapies or combination therapies containing the following compounds: Statins [Atorvastatin (Lipitor®, Sortis®), Fluvastatin (Lescol®), Lovastatin (Mevacor®, Altoprev™), Pravastatin (Pravachol®), Pitavastatin (Livalo®, Lipostat®), Simvastatin (Zocor® or Vytorin® or Inegy® where simvastatin dose was less than 40 mg), Rosuvastatin (Crestor®)]; selective cholesterol and/or bile acid absorption inhibitors [Cholestyramine/Colestyramine (Questran®, Questran Light®, Prevalite®, Locholest®, Locholest® Light), Colestipol (Colestid®), Colesevelam hydrochloride (Welchol®, Cholestagel®), or Ezetimibe (Zetia®, Ezetrol®)]; Fibrates [Fenofibrate (Antara®, Lofibra®, Tricor®, Triglide™, Lipantil®, Supralip®), Bezafibrate (Bezalip®), or Ciprofibrate (Modalim®)]; Approved PCSK9 inhibitors were excluded at entry criteria but allowed as adjunctive therapy beginning at Week 24 if LDL-C threshold criteria was met as described in the protocol. Gemfibrozil, a fibrate, was prohibited. Other concomitant medications were allowed but must have been stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety. Participants were not allowed to use some medications (monotherapies or combination therapies) within 4 weeks prior to screening or during the study.

Evidence for comparator:

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

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 21 January 2016 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Germany: 269        |
| Country: Number of subjects enrolled | Netherlands: 162    |
| Country: Number of subjects enrolled | Poland: 571         |
| Country: Number of subjects enrolled | United Kingdom: 462 |

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

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 877  |
| From 65 to 84 years                       | 1333 |
| 85 years and over                         | 20   |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

The study consisted of 2 periods: a 2-week screening period and a 52-week double-blind, randomized treatment period.

### Period 1

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

Blinding implementation details:

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

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

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

Dosage and administration details:

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

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Bempedoic acid |
|------------------|----------------|

Arm description:

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

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

Dosage and administration details:

Participants received bempedoic acid 180 mg tablet, once-daily by mouth for 52 weeks during the

double-blind treatment period.

| <b>Number of subjects in period 1</b> | Placebo | Bempedoic acid |
|---------------------------------------|---------|----------------|
| Started                               | 742     | 1488           |
| Completed                             | 706     | 1404           |
| Not completed                         | 36      | 84             |
| Physician decision                    | -       | 1              |
| Adverse event, non-fatal              | 12      | 37             |
| Protocol violation                    | -       | 2              |
| Withdrawal by participant             | 23      | 40             |
| Unknown                               | -       | 1              |
| Lost to follow-up                     | 1       | 2              |
| Sponsor decision                      | -       | 1              |

## Baseline characteristics

### Reporting groups

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

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

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

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



## End points

### End points reporting groups

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

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

|  |  |
|--|--|
| End point title  | Percentage of Participants With Treatment-emergent Adverse Events (TEAEs) <sup>[1]</sup> |
| End point description:<br>TEAEs, defined as adverse events (AEs) that began or worsened in severity after the first dose of double-blind study drug and up to 30 days after receiving the last dose of double-blind study drug, were collected and reported. |  |
| End point type   | Primary  |
| End point timeframe:<br>Up to approximately 52 weeks   |  |
| Notes:<br>[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.<br>Justification: The statistical analysis was descriptive in nature.          |  |

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

|   |  |
|---|--|
| Notes:<br>[2] - Safety Population (SP) included all randomized patients who received at least 1 dose of study drug.<br>[3] - SP |  |
|---|--|

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants With Adjudicated Major Adverse Cardiovascular Event

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Adjudicated Major Adverse |
|-----------------|---|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[5] - SP

[6] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Creatine Kinase Elevations <sup>[7]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[8] - SP

[9] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Hepatic Disorders <sup>[10]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[11] - SP

[12] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Hypoglycemia <sup>[13]</sup> |
|-----------------|---|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[14] - SP

[15] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Metabolic Acidosis <sup>[16]</sup> |
|-----------------|---|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[17] - SP

[18] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Muscular Disorder <sup>[19]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[20] - SP

[21] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Neurocognitive Disorder <sup>[22]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[23] - SP

[24] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: New Onset or Worsening Diabetes Mellitus <sup>[25]</sup> |
|-----------------|---|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[26] - SP

[27] - SP

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With the Indicated Event of Special Interest: Renal Disorder <sup>[28]</sup> |
|-----------------|---|

End point description:

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

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

End point timeframe:

Up to approximately 52 weeks

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[29] - SP

[30] - SP

### Statistical analyses

No statistical analyses for this end point

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

|   |  |
|---|--|
| End point title   | Change From Baseline to Week 52 in Uric Acid Level <sup>[31]</sup> |
| End point description:  |  |
| Blood samples were drawn at defined time points during the course of the study to monitor uric acid levels. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Baseline and Week 52  |  |

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[32] - SP

[33] - SP

### Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline to Week 52 in Creatinine Level



|  |   |
|--|---|
| End point title  | Change From Baseline to Week 52 in Creatinine Level <sup>[34]</sup> |
| End point description:<br>Blood samples were drawn at defined time points during the course of the study to monitor creatinine levels. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline and Week 52   |   |

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[35] - SP

[36] - SP

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline to Week 52 in Hemoglobin Level

|  |   |
|--|---|
| End point title  | Change From Baseline to Week 52 in Hemoglobin Level <sup>[37]</sup> |
| End point description:<br>Blood samples were drawn at defined time points during the course of the study to monitor hemoglobin levels. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline and Week 52   |   |

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive in nature.

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

Notes:

[38] - SP

[39] - SP

## Statistical analyses

**Secondary: Percent Change From Baseline to Week 12 in Low-density Lipoprotein Cholesterol (LDL-C)**

|  |  |
|--|--|
| End point title  | Percent Change From Baseline to Week 12 in Low-density Lipoprotein Cholesterol (LDL-C) |
| End point description:   |  |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for LDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(LDL-C value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen. Least Square mean= LS mean. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Week 12  |  |

| End point values                    | Placebo             | Bempedoic acid       |  |  |
|-------------------------------------|---------------------|----------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed         | 742 <sup>[40]</sup> | 1488 <sup>[41]</sup> |  |  |
| Units: percent change               |                     |                      |  |  |
| least squares mean (standard error) | 1.6 (± 0.86)        | -16.5 (± 0.52)       |  |  |

Notes:

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

[41] - FAS

**Statistical analyses**

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Difference [BA - placebo] in LS mean at Week 12 |
| Statistical analysis description:  |   |
| The percentage change from baseline were analyzed with the use of analysis of covariance (ANCOVA), with treatment group and randomization strata as factors and baseline lipid value as a covariate. |   |
| Comparison groups  | Placebo v Bempedoic acid                        |
| Number of subjects included in analysis  | 2230  |
| Analysis specification   | Pre-specified                                   |
| Analysis type  | superiority                                     |
| P-value  | < 0.001   |
| Method   | ANCOVA  |
| Parameter estimate   | Difference in LS mean                           |
| Point estimate   | -18.1   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -20   |
| upper limit  | -16.1   |
| Variability estimate   | Standard error of the mean                      |
| Dispersion value   | 1.01  |

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

|                 |   |
|-----------------|---|
| End point title | Absolute Change From Baseline to Week 12 in LDL-C |
|-----------------|---|

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for LDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Absolute change from baseline was calculated as: LDL-C value at Week 12 minus Baseline value. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen.

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

End point timeframe:

Week 12

| End point values                     | Placebo             | Bempedoic acid       |  |  |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed          | 742 <sup>[42]</sup> | 1488 <sup>[43]</sup> |  |  |
| Units: mg/dL                         |                     |                      |  |  |
| arithmetic mean (standard deviation) |                     |                      |  |  |
| Week 12 (n = 725, 1424)              | 0.43 (± 27.036)     | -19.23 (± 24.005)    |  |  |

Notes:

[42] - FAS

[43] - FAS

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Percent Change From Baseline to Week 24 in LDL-C

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline to Week 24 in LDL-C |
|-----------------|--|

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for LDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(LDL-C value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 24

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

Notes:

[44] - FAS

[45] - FAS

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Difference [BA - placebo] in LS mean at Week 24 |
| Statistical analysis description:<br>The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate. |   |
| Comparison groups  | Placebo v Bempedoic acid                        |
| Number of subjects included in analysis  | 2230  |
| Analysis specification   | Pre-specified                                   |
| Analysis type  | superiority                                     |
| P-value  | < 0.001   |
| Method   | ANCOVA  |
| Parameter estimate   | Difference in LS mean                           |
| Point estimate   | -16.1   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -18.2   |
| upper limit  | -14   |
| Variability estimate   | Standard error of the mean                      |
| Dispersion value   | 1.07  |

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

|  |   |
|--|---|
| End point title  | Percent Change From Baseline to Week 12 in Non-high-density Lipoprotein Cholesterol (non-HDL-C) |
| End point description:<br>Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for non-HDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(non-HDL-C value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen. |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Week 12  |   |

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

Notes:

[46] - FAS

[47] - FAS

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Difference [BA - placebo] in LS mean at Week 12 |
| Statistical analysis description:<br>The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate. |   |
| Comparison groups  | Placebo v Bempedoic acid                        |
| Number of subjects included in analysis  | 2230  |
| Analysis specification   | Pre-specified                                   |
| Analysis type  | superiority                                     |
| P-value  | < 0.001   |
| Method   | ANCOVA  |
| Parameter estimate   | Difference in LS mean                           |
| Point estimate   | -13.3   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -15.1   |
| upper limit  | -11.6   |
| Variability estimate   | Standard error of the mean                      |
| Dispersion value   | 0.9   |

### Other pre-specified: Percent Change From Baseline to Week 12 in Total Cholesterol (TC)

|  |   |
|--|---|
| End point title  | Percent Change From Baseline to Week 12 in Total Cholesterol (TC) |
| End point description:<br>Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for TC. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(TC value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen. |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Week 12  |   |

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

Notes:

[48] - FAS

[49] - FAS

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Difference [BA - placebo] in LS mean at Week 12 |
| Statistical analysis description:<br>The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and |   |

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

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

### Other pre-specified: Percent Change From Baseline to Week 12 in Apolipoprotein B (apoB)

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

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for apoB. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(apoB value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Missing data were imputed with the use of a pattern-mixture model to account for adherence to the trial regimen

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 12

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

Notes:

[50] - FAS

[51] - FAS

### Statistical analyses

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

Statistical analysis description:

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

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

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

### Other pre-specified: Percent Change From Baseline to Week 12 in High-sensitivity C-reactive Protein (hsCRP)

|   |  |
|---|--|
| End point title   | Percent Change From Baseline to Week 12 in High-sensitivity C-reactive Protein (hsCRP) |
| End point description:  |  |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for hsCRP. Baseline was defined as the last value prior to first dose of IMP. Percent change from baseline was calculated as: [(hsCRP value at Week 12 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |  |
| End point type  | Other pre-specified  |
| End point timeframe:  |  |
| Week 12   |  |

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

Notes:

[52] - FAS

[53] - FAS

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Difference [BA - placebo] in LS mean at Week 12 |
| Statistical analysis description:  |   |
| The percentage change from baseline was analyzed with the use of a nonparametric approach, P values are from the Wilcoxon rank-sum test, and location shift and confidence interval from the Hodges-Lehmann estimates. |   |
| Comparison groups  | Placebo v Bempedoic acid                        |

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

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline to Week 52 in LDL-C |
| End point description:   |  |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for LDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(LDL-C value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |  |
| End point type   | Other pre-specified                              |
| End point timeframe:   |  |
| Week 52  |  |

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

Notes:

[54] - FAS

[55] - FAS

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Difference [BA - placebo] in LS mean at Week 52 |
| Statistical analysis description:   |   |
| The percentage change from baseline were analyzed with the use of ANCOVA, with treatment group and randomization strata as factors and baseline lipid value as a covariate. |   |
| Comparison groups   | Placebo v Bempedoic acid                        |



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

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline to Week 24 in non-HDL-C |
| End point description:   |  |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for non-HDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(non-HDL-C value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |  |
| End point type   | Other pre-specified                                  |
| End point timeframe:   |  |
| Week 24  |  |

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

Notes:

[56] - FAS

[57] - FAS

### Statistical analyses

No statistical analyses for this end point

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline to Week 52 in non-HDL-C |
| End point description:   |  |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for non-HDL-C. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(non-HDL-C |  |

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

|                      |                     |
|----------------------|---------------------|
| End point type       | Other pre-specified |
| End point timeframe: |                     |
| Week 52              |                     |

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

Notes:

[58] - FAS

[59] - FAS

## Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | Percent Change From Baseline to Week 24 in TC |
| End point description:   |   |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for TC. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(TC value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |   |
| End point type   | Other pre-specified                           |
| End point timeframe:   |   |
| Week 24  |   |

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

Notes:

[60] - FAS

[61] - FAS

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline to Week 52 in TC |
|-----------------|---|

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for TC. Baseline was defined as the mean of the values at screening and predose Day 1/Week 0. Percent change from baseline was calculated as: [(TC value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 52

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

Notes:

[62] - FAS

[63] - FAS

**Statistical analyses**

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline to Week 24 in apoB |
|-----------------|---|

End point description:

Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for apoB. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(apoB value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 24

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

Notes:

[64] - FAS

[65] - FAS

## Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | Percent Change From Baseline to Week 52 in apoB |
| End point description:<br>Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for apoB. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(apoB value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |   |
| End point type   | Other pre-specified                             |
| End point timeframe:<br>Week 52  |   |

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

Notes:

[66] - FAS

[67] - FAS

## Statistical analyses

No statistical analyses for this end point

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline to Week 24 in hsCRP |
| End point description:<br>Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for hsCRP. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(hsCRP value at Week 24 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |  |
| End point type   | Other pre-specified                              |
| End point timeframe:<br>Week 24  |  |

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

Notes:

[68] - FAS

[69] - FAS

### Statistical analyses

No statistical analyses for this end point

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline to Week 52 in hsCRP |
| End point description:   |  |
| Blood samples were drawn after a minimum 10-hour fast (water was allowed) at pre-specified intervals. Samples were collected and analyzed for hsCRP. Baseline was defined as the last value prior to first dose of study drug. Percent change from baseline was calculated as: [(hsCRP value at Week 52 minus Baseline value) divided by (Baseline Value)] multiplied by 100. Observed data was used for the analysis, no imputation for the missing data was performed. |  |
| End point type   | Other pre-specified                              |
| End point timeframe:   |  |
| Week 52  |  |

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

Notes:

[70] - FAS

[71] - FAS

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 12, Week 24, and Week 52

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

Notes:

[72] - FAS

[73] - FAS

## Statistical analyses

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

Statistical analysis description:

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

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

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 52 weeks

Adverse event reporting additional description:

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

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Bempedoic Acid |
|-----------------------|----------------|

Reporting group description: -

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

Reporting group description: -

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

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



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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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



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

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

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

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

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

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

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pain in extremity                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rotator cuff syndrome                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Abscess jaw                                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 1487 (0.00%) | 1 / 742 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal sepsis                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Appendicitis                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchitis                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 1 / 742 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Campylobacter gastroenteritis                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Clostridium difficile infection                 |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cellulitis                                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 1487 (0.13%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Erysipelas                                      |                  |                 |  |
| subjects affected / exposed                     | 3 / 1487 (0.20%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticulitis                                  |                  |                 |  |
| subjects affected / exposed                     | 4 / 1487 (0.27%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastroenteritis                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Helicobacter infection                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1487 (0.00%) | 1 / 742 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Implant site infection                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1487 (0.00%) | 1 / 742 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infected bite                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infective aneurysm                              |                  |                 |  |



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

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

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

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1487 (0.00%) | 1 / 742 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperkalaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 2 / 1487 (0.13%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyponatraemia                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1487 (0.00%) | 1 / 742 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1487 (0.07%) | 0 / 742 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Bempedoic Acid      | Placebo            |  |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                     |                    |  |
| subjects affected / exposed                           | 792 / 1487 (53.26%) | 381 / 742 (51.35%) |  |
| Investigations  |                     |                    |  |
| Blood creatine phosphokinase increased                |                     |                    |  |
| subjects affected / exposed                           | 35 / 1487 (2.35%)   | 13 / 742 (1.75%)   |  |
| occurrences (all)                                     | 36                  | 14                 |  |
| Vascular disorders                                    |                     |                    |  |
| Hypertension  |                     |                    |  |
| subjects affected / exposed                           | 42 / 1487 (2.82%)   | 26 / 742 (3.50%)   |  |
| occurrences (all)                                     | 44                  | 27                 |  |
| Cardiac disorders                                     |                     |                    |  |
| Angina pectoris                                       |                     |                    |  |
| subjects affected / exposed                           | 24 / 1487 (1.61%)   | 19 / 742 (2.56%)   |  |
| occurrences (all)                                     | 27                  | 22                 |  |
| Nervous system disorders                              |                     |                    |  |

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 28 January 2016   | <p>Protocol Amendment 1 dated 28 January 2016- Major changes to the protocol with this amendment included:</p> <ul style="list-style-type: none"><li>• Addition of secondary and tertiary study objectives to evaluate lipid and cardiometabolic parameters at specific time points throughout the study</li><li>• Addition of protocol requirements to address the recent marketing of proprotein convertase subtilisin kexin type 9i (PCSK9i) therapies resulting in the addition of exclusion criteria, prohibited medications instructions, and allowable medication instructions to reflect the protocol requirements</li><li>• Defined clinical endpoints to provide clarity regarding the events that will be adjudicated by the clinical event committee</li><li>• Revised the reporting requirements for clinical endpoints</li><li>• Revised inclusion/exclusion criteria by aligning the medical history and concurrent conditions of the study population with those commonly observed in participants with hyperlipidemia and high cardiovascular risk</li><li>• Revised safety monitoring and management instructions to ensure participant safety for the following:<ul style="list-style-type: none"><li>– elevated serum creatinine</li><li>– hemoglobin</li><li>– elevated creatine kinase</li><li>– low-density lipoprotein cholesterol threshold criteria for the addition of adjunctive therapy beginning at Week 24 (Visit T5)</li><li>– hypoglycemia</li></ul></li></ul>   |
| 09 March 2016     | <p>Protocol Amendment 2 dated 23 February 2016- The major changes to the protocol with this amendment was for program consistency, revision of severity categories for adverse events to the 3 categories of severity.</p>  |
| 09 September 2016 | <p>Protocol Amendment 3 dated 28 July 2016- Major changes to the protocol with this amendment included:</p> <ul style="list-style-type: none"><li>• Increased sample size from 900 to 1950 randomized participants</li><li>• Revised the high-dose statin exclusion to allow participants on high-dose statins with the exception of participants on simvastatin taking average daily doses that were greater than 40 mg. This revision was based upon the weak drug interactions observed with bempedoic acid 240 mg when given with low-dose statins.</li><li>• Increased overall study duration to account for additional recruitment time required to randomize additional participants</li><li>• Revised inclusion criteria to be consistent with current safety data and to comply with Health Canada requests<ul style="list-style-type: none"><li>– Revised to include tubal ligation in the study definition for “surgically sterile.”</li><li>– Revised to include the birth control requirement as requested by Health Canada. This revision only applied to Canadian sites</li></ul></li><li>• Revised exclusion criteria to be consistent with current safety data. Revisions included:<ul style="list-style-type: none"><li>– Increased total fasting triglycerides, decreased the estimated glomerular filtration rate (eGFR), Allowed participants with positive hepatitis C-antibodies (HCV-AB) results to have a reflex HCV RNA performed so that those participants without active disease may have been considered for enrolment, allowed participants whose total bilirubin levels exceeded <math>\geq 1.2 \times</math> Upper limit normal to have a reflex indirect (unconjugated) bilirubin test so that those participants with results that were consistent with Gilbert’s disease, shortened the duration from when a participant may have had, for any reason, a blood transfusion, decreased the amount of time participants should be stable on obesity medications, removed the collection of blood samples for pharmacokinetic assessment for those participants who were randomized into the study after the implementation of Protocol Amendment 3.</li></ul></li></ul> |



|                  |   |
|------------------|---|
| 06 December 2016 | <p>Protocol Amendment 4 dated 14 October 2016- Major changes to the protocol with this amendment included:</p> <ul style="list-style-type: none"> <li>• Revised exclusion criteria to be consistent with current safety data and to comply with US Food and Drug Administration (FDA) request. Excluded renally impaired participants receiving an average daily dose of simvastatin 40 mg with eGFR &lt;45 milliliter per minute per 1.73 square meter (mL/min/1.73<sup>m2</sup>).</li> <li>• To comply with US FDA request, additional visits (2 in the clinic and 2 by telephone) were added for clinical safety laboratory evaluations and adverse event monitoring for participants receiving an average daily dose of simvastatin 40 mg</li> </ul>  |
| 03 July 2017     | <p>Protocol Amendment 5 dated 10 May 2017- Major changes to the protocol with this amendment included:</p> <ul style="list-style-type: none"> <li>• Simvastatin at average daily doses of 40 mg or greater was added as a prohibited medication.</li> <li>• Revised the collection of reserve samples to allow Sponsor to discontinue collection after a sufficient number of samples were collected</li> <li>• Revised procedures for Visits T4.1, T4.2, T5.1, and T5.2 to indicate that participants who were discontinued from study drug because they were on simvastatin 40 mg or greater and who provided consent to be followed in the safety follow-up should be scheduled for these visits</li> <li>• Added a procedure to Visit T7 for participants who completed the study while taking study drug to collect information regarding whether: 1) the participant was offered the open-label extension study (Study 1002-050) and 2) if not, the reason that the open-label extension study was not offered to the participant</li> <li>• To further ensure participant safety, the monitoring and management of creatine kinase (CK) was revised to include additional instructions for the investigator in cases where the repeat CK was confirmed to be greater than 5 × upper limit of normal (ULN) and the participant was asymptomatic.</li> </ul> |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30865796>