



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled and Delayed-Start Study of LY3314814 in Mild Alzheimer's Disease Dementia (The DAYBREAK Study)

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2015-005625-39             |
| Trial protocol           | GB PT ES PL CZ DK NL FR IT |
| Global end of trial date | 28 September 2018          |

#### Results information

|                                |                                                              |
|--------------------------------|--------------------------------------------------------------|
| Result version number          | v2 (current)                                                 |
| This version publication date  | 15 August 2019                                               |
| First version publication date | 27 June 2019                                                 |
| Version creation reason        | • Correction of full data set<br>Correction of full data set |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | I8D-MC-AZET |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT02783573         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | Trial Number: 16024 |

Notes:

#### Sponsors

|                              |                                                                               |
|------------------------------|-------------------------------------------------------------------------------|
| Sponsor organisation name    | Eli Lilly and Company                                                         |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285                |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,     |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,     |
| Sponsor organisation name    | AstraZeneca UK Limited                                                        |
| Sponsor organisation address | Charter Way, Macclesfield, Cheshire, United Kingdom, SK10 2NA                 |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, AstraZeneca UK Limited, 44 1625-58-2828, |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, AstraZeneca UK Limited, 44 1625-58-2828, |

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 September 2018 |
| Is this the analysis of the primary completion data? | No                |

|                                  |                   |
|----------------------------------|-------------------|
| Global end of trial reached?     | Yes               |
| Global end of trial date         | 28 September 2018 |
| Was the trial ended prematurely? | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of the study drug known as lanabecestat in participants with mild Alzheimer's disease (AD) dementia.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 01 July 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 | Czech Republic: 129     |
| Country: Number of subjects enrolled | United States: 600      |
| Country: Number of subjects enrolled | Japan: 119              |
| Country: Number of subjects enrolled | United Kingdom: 68      |
| Country: Number of subjects enrolled | Portugal: 24            |
| Country: Number of subjects enrolled | Russian Federation: 100 |
| Country: Number of subjects enrolled | Spain: 78               |
| Country: Number of subjects enrolled | Canada: 96              |
| Country: Number of subjects enrolled | Korea, Republic of: 59  |
| Country: Number of subjects enrolled | Netherlands: 30         |
| Country: Number of subjects enrolled | China: 2                |
| Country: Number of subjects enrolled | Taiwan: 24              |
| Country: Number of subjects enrolled | Poland: 122             |
| Country: Number of subjects enrolled | Denmark: 23             |
| Country: Number of subjects enrolled | Italy: 66               |
| Country: Number of subjects enrolled | Mexico: 29              |

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 93  |
| Country: Number of subjects enrolled | Germany: 60 |
| Worldwide total number of subjects   | 1722        |
| EEA total number of subjects         | 693         |

Notes:

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### Subjects enrolled per age group

|                                           |      |
|-------------------------------------------|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 257  |
| From 65 to 84 years                       | 1435 |
| 85 years and over                         | 30   |

## Subject disposition

### Recruitment

Recruitment details:

No Text Available

### Pre-assignment

Screening details:

In Period 1, per the protocol, placebo-controlled groups (Placebo for 78 weeks then Lanabecestat 20 mg; Placebo for 78 weeks then Lanabecestat 50 mg) were combined to form one placebo group. As study terminated early and very few participants entered into the period 2, the arms in period 2 are combined based on dose exposure for ease of comparison.

### Period 1

|                              |                              |
|------------------------------|------------------------------|
| Period 1 title               | Placebo-Controlled Period    |
| Is this the baseline period? | Yes                          |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

### Arms

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

Arm description:

Participants received placebo film-coated oral tablets once daily.

|                                        |                    |
|----------------------------------------|--------------------|
| 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:

Film-coated tablets of placebo administered orally once a day.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Lanabecestat 20 mg |
|------------------|--------------------|

Arm description:

Participants received lanabecestat 20 mg film-coated oral tablets once daily.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Lanabecestat       |
| Investigational medicinal product code |                    |
| Other name                             | LY3314814, AZD3293 |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

20 mg film-coated tablets of lanabecestat administered orally once a day.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Lanabecestat 50 mg |
|------------------|--------------------|

Arm description:

Participants received lanabecestat 50 mg film-coated oral tablets once daily.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Lanabecestat       |
| Investigational medicinal product code |                    |
| Other name                             | LY3314814, AZD3293 |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

50 mg film-coated tablets of lanabecestat administered orally once a day.

| <b>Number of subjects in period 1</b>    | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg |
|------------------------------------------|---------|--------------------|--------------------|
| Started                                  | 562     | 590                | 570                |
| Received at Least 1 Dose of Study Drug   | 558     | 588                | 568                |
| Completed                                | 26      | 28                 | 22                 |
| Not completed                            | 536     | 562                | 548                |
| Adverse event, serious fatal             | 4       | 2                  | 3                  |
| Consent withdrawn by subject             | 15      | 20                 | 23                 |
| Physician decision                       | 3       | 1                  | 3                  |
| Non-Compliance                           | -       | 1                  | -                  |
| Adverse event, non-fatal                 | 13      | 17                 | 13                 |
| Withdrawal due to Caregiver Circumstance | 3       | 3                  | 9                  |
| Other-selected by Investigator           | -       | 1                  | 2                  |
| Sponsor Decision                         | 494     | 512                | 492                |
| Lost to follow-up                        | 3       | 3                  | 1                  |
| Protocol deviation                       | 1       | 2                  | -                  |
| Lack of efficacy                         | -       | -                  | 2                  |

## Period 2

|                              |                              |
|------------------------------|------------------------------|
| Period 2 title               | Delayed-Start Period         |
| Is this the baseline period? | No                           |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

## Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                                                                                                      |                    |
|------------------------------------------------------------------------------------------------------|--------------------|
| <b>Arm title</b>                                                                                     | Lanabecestat 20 mg |
| Arm description:<br>Participants received lanabecestat 20 mg film-coated oral tablets once daily.    |                    |
| Arm type                                                                                             | Experimental       |
| Investigational medicinal product name                                                               | Lanabecestat       |
| Investigational medicinal product code                                                               |                    |
| Other name                                                                                           | LY3314814, AZD3293 |
| Pharmaceutical forms                                                                                 | Film-coated tablet |
| Routes of administration                                                                             | Oral use           |
| Dosage and administration details:<br>20 mg film-coated tablets of lanabecestat administered orally. |                    |

|                                                                                                      |                    |
|------------------------------------------------------------------------------------------------------|--------------------|
| <b>Arm title</b>                                                                                     | Lanabecestat 50 mg |
| Arm description:<br>Participants received lanabecestat 50 mg film-coated oral tablets once daily.    |                    |
| Arm type                                                                                             | Experimental       |
| Investigational medicinal product name                                                               | Lanabecestat       |
| Investigational medicinal product code                                                               |                    |
| Other name                                                                                           | LY3314814, AZD3293 |
| Pharmaceutical forms                                                                                 | Film-coated tablet |
| Routes of administration                                                                             | Oral use           |
| Dosage and administration details:<br>50 mg film-coated tablets of lanabecestat administered orally. |                    |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Lanabecestat 20 mg | Lanabecestat 50 mg |
|-----------------------------------------------------|--------------------|--------------------|
| Started                                             | 17                 | 12                 |
| Received at Least 1 Dose of Study Drug              | 14                 | 12                 |
| Completed                                           | 0                  | 0                  |
| Not completed                                       | 17                 | 12                 |
| Sponsor Decision                                    | 17                 | 12                 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients who completed period 1 may not have entered period 2 due to early termination of the study.

## Baseline characteristics

### Reporting groups

|                                                                               |                    |
|-------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                         | Placebo            |
| Reporting group description:                                                  |                    |
| Participants received placebo film-coated oral tablets once daily.            |                    |
| Reporting group title                                                         | Lanabecestat 20 mg |
| Reporting group description:                                                  |                    |
| Participants received lanabecestat 20 mg film-coated oral tablets once daily. |                    |
| Reporting group title                                                         | Lanabecestat 50 mg |
| Reporting group description:                                                  |                    |
| Participants received lanabecestat 50 mg film-coated oral tablets once daily. |                    |

| Reporting group values                             | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg |
|----------------------------------------------------|---------|--------------------|--------------------|
| Number of subjects                                 | 562     | 590                | 570                |
| Age categorical                                    |         |                    |                    |
| Units: Subjects                                    |         |                    |                    |
| In utero                                           |         |                    |                    |
| Preterm newborn infants (gestational age < 37 wks) |         |                    |                    |
| Newborns (0-27 days)                               |         |                    |                    |
| Infants and toddlers (28 days-23 months)           |         |                    |                    |
| Children (2-11 years)                              |         |                    |                    |
| Adolescents (12-17 years)                          |         |                    |                    |
| Adults (18-64 years)                               |         |                    |                    |
| From 65-84 years                                   |         |                    |                    |
| 85 years and over                                  |         |                    |                    |
| Age continuous                                     |         |                    |                    |
| Units: years                                       |         |                    |                    |
| arithmetic mean                                    | 72.1    | 72.3               | 72.6               |
| standard deviation                                 | ± 7.1   | ± 7.0              | ± 7.0              |
| Gender categorical                                 |         |                    |                    |
| Units: Subjects                                    |         |                    |                    |
| Female                                             | 348     | 335                | 340                |
| Male                                               | 214     | 255                | 230                |
| Ethnicity (NIH/OMB)                                |         |                    |                    |
| Units: Subjects                                    |         |                    |                    |
| Hispanic or Latino                                 | 53      | 45                 | 55                 |
| Not Hispanic or Latino                             | 416     | 442                | 423                |
| Unknown or Not Reported                            | 93      | 103                | 92                 |
| Race (NIH/OMB)                                     |         |                    |                    |
| Units: Subjects                                    |         |                    |                    |
| American Indian or Alaska Native                   | 5       | 7                  | 6                  |
| Asian                                              | 64      | 76                 | 69                 |
| Native Hawaiian or Other Pacific Islander          | 0       | 1                  | 3                  |
| Black or African American                          | 4       | 5                  | 9                  |
| White                                              | 387     | 398                | 389                |
| More than one race                                 | 72      | 70                 | 62                 |

|                                                                                                                                                                                                                      |       |       |       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-------|
| Unknown or Not Reported                                                                                                                                                                                              | 30    | 33    | 32    |
| Region of Enrollment                                                                                                                                                                                                 |       |       |       |
| Units: Subjects                                                                                                                                                                                                      |       |       |       |
| United States                                                                                                                                                                                                        | 196   | 205   | 199   |
| Japan                                                                                                                                                                                                                | 38    | 43    | 38    |
| United Kingdom                                                                                                                                                                                                       | 23    | 22    | 23    |
| Portugal                                                                                                                                                                                                             | 8     | 8     | 8     |
| Russia                                                                                                                                                                                                               | 33    | 36    | 31    |
| Spain                                                                                                                                                                                                                | 25    | 25    | 28    |
| Canada                                                                                                                                                                                                               | 32    | 33    | 31    |
| South Korea                                                                                                                                                                                                          | 19    | 20    | 20    |
| Netherlands                                                                                                                                                                                                          | 9     | 9     | 12    |
| China                                                                                                                                                                                                                | 1     | 0     | 1     |
| Taiwan                                                                                                                                                                                                               | 5     | 10    | 9     |
| Poland                                                                                                                                                                                                               | 39    | 43    | 40    |
| Denmark                                                                                                                                                                                                              | 7     | 8     | 8     |
| Italy                                                                                                                                                                                                                | 23    | 22    | 21    |
| Mexico                                                                                                                                                                                                               | 11    | 9     | 9     |
| France                                                                                                                                                                                                               | 30    | 33    | 30    |
| Germany                                                                                                                                                                                                              | 21    | 22    | 17    |
| Czech Republic                                                                                                                                                                                                       | 42    | 42    | 45    |
| ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale)                                                                                                                                                            |       |       |       |
| ADAS-Cog13, a 13-item rating scale, measured the severity of cognitive dysfunction in persons with Alzheimer's disease (AD). Scores ranged from 0 to 85, with a higher score indicating worse cognitive functioning. |       |       |       |
| Units: Units on a Scale                                                                                                                                                                                              |       |       |       |
| arithmetic mean                                                                                                                                                                                                      | 30.4  | 30.6  | 30.6  |
| standard deviation                                                                                                                                                                                                   | ± 7.9 | ± 8.3 | ± 8.5 |

|                                                    |       |  |  |
|----------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                      | Total |  |  |
| Number of subjects                                 | 1722  |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 0     |  |  |
| From 65-84 years                                   | 0     |  |  |
| 85 years and over                                  | 0     |  |  |
| Age continuous                                     |       |  |  |
| Units: years                                       |       |  |  |
| arithmetic mean                                    |       |  |  |
| standard deviation                                 | -     |  |  |
| Gender categorical                                 |       |  |  |
| Units: Subjects                                    |       |  |  |
| Female                                             | 1023  |  |  |
| Male                                               | 699   |  |  |



|                                                                                                                                                                                                                      |      |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--|--|
| Ethnicity (NIH/OMB)                                                                                                                                                                                                  |      |  |  |
| Units: Subjects                                                                                                                                                                                                      |      |  |  |
| Hispanic or Latino                                                                                                                                                                                                   | 153  |  |  |
| Not Hispanic or Latino                                                                                                                                                                                               | 1281 |  |  |
| Unknown or Not Reported                                                                                                                                                                                              | 288  |  |  |
| Race (NIH/OMB)                                                                                                                                                                                                       |      |  |  |
| Units: Subjects                                                                                                                                                                                                      |      |  |  |
| American Indian or Alaska Native                                                                                                                                                                                     | 18   |  |  |
| Asian                                                                                                                                                                                                                | 209  |  |  |
| Native Hawaiian or Other Pacific Islander                                                                                                                                                                            | 4    |  |  |
| Black or African American                                                                                                                                                                                            | 18   |  |  |
| White                                                                                                                                                                                                                | 1174 |  |  |
| More than one race                                                                                                                                                                                                   | 204  |  |  |
| Unknown or Not Reported                                                                                                                                                                                              | 95   |  |  |
| Region of Enrollment                                                                                                                                                                                                 |      |  |  |
| Units: Subjects                                                                                                                                                                                                      |      |  |  |
| United States                                                                                                                                                                                                        | 600  |  |  |
| Japan                                                                                                                                                                                                                | 119  |  |  |
| United Kingdom                                                                                                                                                                                                       | 68   |  |  |
| Portugal                                                                                                                                                                                                             | 24   |  |  |
| Russia                                                                                                                                                                                                               | 100  |  |  |
| Spain                                                                                                                                                                                                                | 78   |  |  |
| Canada                                                                                                                                                                                                               | 96   |  |  |
| South Korea                                                                                                                                                                                                          | 59   |  |  |
| Netherlands                                                                                                                                                                                                          | 30   |  |  |
| China                                                                                                                                                                                                                | 2    |  |  |
| Taiwan                                                                                                                                                                                                               | 24   |  |  |
| Poland                                                                                                                                                                                                               | 122  |  |  |
| Denmark                                                                                                                                                                                                              | 23   |  |  |
| Italy                                                                                                                                                                                                                | 66   |  |  |
| Mexico                                                                                                                                                                                                               | 29   |  |  |
| France                                                                                                                                                                                                               | 93   |  |  |
| Germany                                                                                                                                                                                                              | 60   |  |  |
| Czech Republic                                                                                                                                                                                                       | 129  |  |  |
| ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale)                                                                                                                                                            |      |  |  |
| ADAS-Cog13, a 13-item rating scale, measured the severity of cognitive dysfunction in persons with Alzheimer's disease (AD). Scores ranged from 0 to 85, with a higher score indicating worse cognitive functioning. |      |  |  |
| Units: Units on a Scale                                                                                                                                                                                              |      |  |  |
| arithmetic mean                                                                                                                                                                                                      |      |  |  |
| standard deviation                                                                                                                                                                                                   | -    |  |  |

## End points

### End points reporting groups

|                                                                               |                    |
|-------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                         | Placebo            |
| Reporting group description:                                                  |                    |
| Participants received placebo film-coated oral tablets once daily.            |                    |
| Reporting group title                                                         | Lanabecestat 20 mg |
| Reporting group description:                                                  |                    |
| Participants received lanabecestat 20 mg film-coated oral tablets once daily. |                    |
| Reporting group title                                                         | Lanabecestat 50 mg |
| Reporting group description:                                                  |                    |
| Participants received lanabecestat 50 mg film-coated oral tablets once daily. |                    |
| Reporting group title                                                         | Lanabecestat 20 mg |
| Reporting group description:                                                  |                    |
| Participants received lanabecestat 20 mg film-coated oral tablets once daily. |                    |
| Reporting group title                                                         | Lanabecestat 50 mg |
| Reporting group description:                                                  |                    |
| Participants received lanabecestat 50 mg film-coated oral tablets once daily. |                    |
| Subject analysis set title                                                    | Lanabecestat       |
| Subject analysis set type                                                     | Per protocol       |
| Subject analysis set description:                                             |                    |
| Participants received Lanabecestat film-coated tablets orally.                |                    |

### Primary: Change from Baseline in Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog13) Score

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Change from Baseline in Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog13) Score |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                     |
| ADAS-Cog13 is a psychometric instrument that evaluates word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration/ distractibility. The total score of the 13-item scale ranges from 0 to 85, with an increase in score indicating cognitive worsening. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with factors for treatment, visit, treatment-by-visit interaction, AChEI (acetylcholinesterase Inhibitor) use at baseline, pooled site, and covariates for baseline ADAS-Cog13 total score, age at baseline, and baseline ADAS-Cog13 total score-by-visit interaction. |                                                                                                     |
| Analysis Population Description (APD): All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADAS-Cog13 measure.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Primary                                                                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                     |
| Baseline, Week 78                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                     |

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 460             | 471                | 464                |  |
| Units: Units on a scale             |                 |                    |                    |  |
| least squares mean (standard error) | 6.42 (± 1.23)   | 8.93 (± 1.11)      | 6.20 (± 1.32)      |  |

## Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | ADAS-Cog13                        |
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 931                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.129                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 2.51                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -0.752                            |
| upper limit                             | 5.776                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.64                              |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | ADAS-Cog13                        |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 924                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.903                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -0.21                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -3.725                            |
| upper limit                             | 3.296                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.76                              |

## Secondary: Change from Baseline in Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items Score (ADCS-iADL)

|                 |                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items Score (ADCS-iADL) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire answered by the participant's caregiver. The ADCS-ADL measures both basic and instrumental activities of daily living by participants. The range for the ADCS-iADL is 0-59 with higher scores reflecting better performance. LS Mean was determined by MMRM model with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline iADL score, age at baseline, and baseline iADL score-by-visit interaction.

APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADCS-iADL measure.

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

End point timeframe:

Baseline, Week 78

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 357             | 369                | 347                |  |
| Units: Units on a scale             |                 |                    |                    |  |
| least squares mean (standard error) | -3.95 (± 1.27)  | -6.91 (± 1.29)     | -7.13 (± 1.40)     |  |

**Statistical analyses**

| Statistical analysis title              | ADCS-iADL                         |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 726                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.1                             |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -2.95                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -6.488                            |
| upper limit                             | 0.58                              |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.78                              |

| Statistical analysis title | ADCS-iADL                    |
|----------------------------|------------------------------|
| Comparison groups          | Placebo v Lanabecestat 50 mg |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 704                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.092                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -3.18                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -6.876                            |
| upper limit                             | 0.525                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.86                              |

## Secondary: Change from Baseline in Functional Activities Questionnaire (FAQ) Score

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Change from Baseline in Functional Activities Questionnaire (FAQ) Score |
|-----------------|-------------------------------------------------------------------------|

### End point description:

FAQ is a 10-item, caregiver-based questionnaire and was administered to the study partner who was asked to rate the participant's ability to perform a variety of activities ranging from writing checks, assembling tax records, shopping, playing games, food preparation, traveling, keeping appointments, traveling out of neighborhood, keeping track of current events and understanding media. FAQ total score was calculated by adding the scores from each of the 10 items. Each activity is rated on a scale from 0 to 3 (Never did and would have difficulty now=1; never did [the activity] but could do now =0; normal =0; has difficulty but does by self =1; requires assistance= 2; Dependent = 3). The maximum FAQ total score is 30, with higher scores indicating greater impairment. LS Mean determined by MMRM model. APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for FAQ score.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 78    |           |

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 358             | 369                | 347                |  |
| Units: Units on a scale             |                 |                    |                    |  |
| least squares mean (standard error) | 3.93 (± 0.81)   | 5.16 (± 0.85)      | 3.41 (± 0.91)      |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | FAQ Score                    |
| Comparison groups          | Placebo v Lanabecestat 20 mg |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 727                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.285                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 1.23                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -1.045                            |
| upper limit                             | 3.499                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.14                              |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | FAQ Score                         |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 705                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.661                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -0.52                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -2.889                            |
| upper limit                             | 1.843                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.19                              |

### Secondary: Change from Baseline on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Change from Baseline on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score |
|-----------------|---------------------------------------------------------------------------------------|

#### End point description:

The iADRS is a composite that measures both cognition and function. The iADRS comprises scores from the ADAS-Cog and the ADCS-iADL. The iADRS is calculated as a linear combination of the total scores of the ADAS-Cog13 (score range 0 to 85 with higher scores reflecting worse performance) and the ADCS-iADL (score range from 0-59 with higher scores reflecting better performance). The iADRS score ranges from 0 to 144 with higher scores indicating greater impairment. LS Mean was determined by MMRM with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline iADRS13 total score, age at baseline, and baseline iADRS13 total score-by-visit interaction.

APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for iADRS.

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

End point timeframe:

Baseline, Week 78

| End point values                    | Placebo                 | Lanabecestat<br>20 mg   | Lanabecestat<br>50 mg   |  |
|-------------------------------------|-------------------------|-------------------------|-------------------------|--|
| Subject group type                  | Reporting group         | Reporting group         | Reporting group         |  |
| Number of subjects analysed         | 342                     | 348                     | 333                     |  |
| Units: Units on a scale             |                         |                         |                         |  |
| least squares mean (standard error) | -10.46 ( $\pm$<br>1.97) | -15.22 ( $\pm$<br>1.90) | -12.43 ( $\pm$<br>2.08) |  |

### Statistical analyses

| Statistical analysis title              | iADRS                             |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 690                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.079                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -4.77                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -10.103                           |
| upper limit                             | 0.56                              |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 2.69                              |

| Statistical analysis title              | iADRS                             |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 675                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.486                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -1.97                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -7.573                            |
| upper limit                             | 3.62                              |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.82                       |

## Secondary: Change from Baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score |
|-----------------|------------------------------------------------------------------------------------|

### End point description:

The CDR-SB is a rater administered scale and impairment is scored in each of categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Impairment is scored on a scale in which no dementia = 0, questionable dementia = 0.5, mild dementia = 1, moderate dementia = 2 and severe dementia = 3. The 6 individual category ratings, or "box scores", were added together to give the CDR-Sum of Boxes which ranges from 0-18, with higher scores indicating greater impairment. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline CDR-SB score, age at baseline, and baseline CDR-SB score-by-visit interaction.

APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CDR-SB.

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

### End point timeframe:

Baseline, Week 78

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 369             | 370                | 363                |  |
| Units: Units on a scale             |                 |                    |                    |  |
| least squares mean (standard error) | 2.32 (± 0.42)   | 2.57 (± 0.41)      | 2.10 (± 0.45)      |  |

## Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | CDR-SB                            |
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 739                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.663                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 0.25                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -0.89                             |
| upper limit                             | 1.391                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.57                              |



|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | CDR-SB                            |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 732                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.717                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -0.22                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -1.423                            |
| upper limit                             | 0.983                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.6                               |

### Secondary: Time to Progression as Measured by Loss of Clinical Dementia Rating (CDR) Global Score Stage

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Time to Progression as Measured by Loss of Clinical Dementia Rating (CDR) Global Score Stage |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                              |
| <p>The CDR global score is a composite score calculated using the Washington University CDR-assignment algorithm applied to the 6 individual domain box scores (Morris 1993). The memory domain is considered the primary category that drives the CDR global outcome, and all other domains are secondary. The CDR global score ranges from 0 to 3 (0 = no dementia, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia).</p> <p>APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CDR global score.</p> |                                                                                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Secondary                                                                                    |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                              |
| From Loss of 1 Global Stage through Week 78                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                              |

| End point values                 | Placebo          | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|----------------------------------|------------------|--------------------|--------------------|--|
| Subject group type               | Reporting group  | Reporting group    | Reporting group    |  |
| Number of subjects analysed      | 479              | 500                | 466                |  |
| Units: Days                      |                  |                    |                    |  |
| median (confidence interval 95%) | 379 (367 to 546) | 367 (365 to 456)   | 449 (365 to 491)   |  |

### Statistical analyses

**Secondary: Change from Baseline in Neuropsychiatric Inventory (NPI) Score**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Change from Baseline in Neuropsychiatric Inventory (NPI) Score |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                |
| <p>The NPI is a questionnaire administered to caregivers that quantifies behavioral changes. Each of the 12 behavioral domains the caregiver reports as present are scored for Frequency, scale: 1 (Occasionally) to 4 (Very Frequently), and Severity, scale: 1 (Mild) to 3 (Severe). If the domain is reported by the caregiver as 'Not Affected,' that domain is scored as 0. The individual domain scores are calculated by multiplying the frequency times the severity for each domain. NPI Total Score is calculated by adding the individual domain scores together for all 12 domains, with a scores range from 0 to 144, with higher scores indicating a greater severity of neuropsychiatric disturbance. LS Mean was determined by MMRM methodology.</p> <p>All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for NPI.</p> |                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                                      |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                |
| Baseline, Week 78                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                |

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 351             | 363                | 342                |  |
| Units: Units on a scale             |                 |                    |                    |  |
| least squares mean (standard error) | 3.45 (± 1.70)   | 3.75 (± 1.84)      | 0.44 (± 1.45)      |  |

**Statistical analyses**

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | NPI                               |
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 714                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.899                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 0.3                               |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -4.297                            |
| upper limit                             | 4.889                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 2.34                              |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | NPI                               |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 693                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.164                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -3.01                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -7.267                            |
| upper limit                             | 1.238                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 2.16                              |

### Secondary: Change from Baseline on the Mini-Mental State Examination (MMSE)

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Change from Baseline on the Mini-Mental State Examination (MMSE) |
|-----------------|------------------------------------------------------------------|

End point description:

The MMSE is an instrument used to assess a participant's global cognitive function. The MMSE assesses orientation to time and place, immediate and delayed recall of words, attention and calculation, language (naming, comprehension and repetition), and spatial ability (copying a figure). The range for MMSE total Score is 0 to 30, with a higher score indicating better cognitive performance. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline MMSE total score, age at baseline, and baseline MMSE total score-by-visit interaction.

APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for MMSE.

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

End point timeframe:

Baseline, Week 78

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 476             | 495                | 477                |  |
| Units: Units on a scale             |                 |                    |                    |  |
| least squares mean (standard error) | -4.16 (± 0.59)  | -5.43 (± 0.58)     | -4.31 (± 0.64)     |  |

### Statistical analyses

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | MMSE                         |
| Comparison groups                 | Placebo v Lanabecestat 20 mg |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 971                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.126                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -1.26                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -2.891                            |
| upper limit                             | 0.362                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.82                              |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | MMSE                              |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 953                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.862                           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -0.15                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -1.867                            |
| upper limit                             | 1.566                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.86                              |

### **Secondary: Percent Change from Baseline in Concentration of Cerebrospinal fluid (CSF) Biomarker A $\beta$ 1-42**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                    | Percent Change from Baseline in Concentration of Cerebrospinal fluid (CSF) Biomarker A $\beta$ 1-42 |
| End point description:<br>Concentration of the peptide A $\beta$ 1-42 in plasma measured by validated immunoassay. LS Mean was determined by Analysis of covariance (ANCOVA) with LOCF (last observation carried forward), terms for treatment, baseline biomarker and age at baseline.<br>APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for A $\beta$ 1-42. |                                                                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                                                                           |
| End point timeframe:<br>Baseline, Week 71                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                     |

| <b>End point values</b>                    | Placebo                 | Lanabecestat<br>20 mg    | Lanabecestat<br>50 mg    |  |
|--------------------------------------------|-------------------------|--------------------------|--------------------------|--|
| Subject group type                         | Reporting group         | Reporting group          | Reporting group          |  |
| Number of subjects analysed                | 4                       | 5                        | 5                        |  |
| Units: Percentage change in A $\beta$ 1-42 |                         |                          |                          |  |
| least squares mean (standard error)        | 23.68 ( $\pm$<br>26.76) | -13.87 ( $\pm$<br>24.30) | -17.04 ( $\pm$<br>23.26) |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | A $\beta$ 1-42                    |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Post-hoc                          |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.343                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -37.55                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -122.35                           |
| upper limit                             | 47.26                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 37.49                             |

| <b>Statistical analysis title</b>       | A $\beta$ 1-42                    |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Post-hoc                          |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.276                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -40.72                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -120.17                           |
| upper limit                             | 38.73                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 35.12                             |

## Secondary: Percent Change from Baseline in Concentration of CSF Biomarker Aβ1-40

|                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                  | Percent Change from Baseline in Concentration of CSF Biomarker Aβ1-40 |
| End point description:<br>Concentration of the peptide Aβ 1-40 in plasma measured by immunoassay. LS Mean was determined by ANCOVA with LOCF (last observation carried forward), terms for treatment, baseline biomarker and age at baseline.<br>APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Aβ1-40. |                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                   | Secondary                                                             |
| End point timeframe:<br>Baseline, Week 71                                                                                                                                                                                                                                                                                                                                                        |                                                                       |

| End point values                    | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 4               | 5                  | 5                  |  |
| Units: Percentage change in Aβ1-40  |                 |                    |                    |  |
| least squares mean (standard error) | 24.52 (± 23.08) | -37.42 (± 20.76)   | -9.63 (± 20.74)    |  |

## Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Statistical analysis title              | Aβ1-40                            |
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Post-hoc                          |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.079                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -61.94                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -132.75                           |
| upper limit                             | 8.87                              |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 31.3                              |

|                            |        |
|----------------------------|--------|
| Statistical analysis title | Aβ1-40 |
|----------------------------|--------|

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Post-hoc                          |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.303                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -34.15                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -104.88                           |
| upper limit                             | 36.59                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 31.27                             |

## Secondary: Change from Baseline in CSF Biomarker Total Tau

|                                                                                                                                                                                                        |                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| End point title                                                                                                                                                                                        | Change from Baseline in CSF Biomarker Total Tau |
| End point description:                                                                                                                                                                                 |                                                 |
| Cerebrospinal fluid samples were collected for analysis of concentration total tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, baseline biomarker and age at baseline. |                                                 |
| APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CSF Total Tau.                                                 |                                                 |
| End point type                                                                                                                                                                                         | Secondary                                       |
| End point timeframe:                                                                                                                                                                                   |                                                 |
| Baseline, Week 71                                                                                                                                                                                      |                                                 |

| End point values                       | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|----------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                     | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed            | 4               | 5                  | 5                  |  |
| Units: Picogram per milliliter (pg/mL) |                 |                    |                    |  |
| least squares mean (standard error)    | 1.84 (± 9.75)   | 18.16 (± 9.77)     | -11.21 (± 9.32)    |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | CSF Total Tau                |
| Comparison groups          | Placebo v Lanabecestat 20 mg |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.283                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 16.32                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -16.015                           |
| upper limit                             | 48.659                            |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 14.29                             |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | CSF Total Tau                     |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.349                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -13.05                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -42.929                           |
| upper limit                             | 16.82                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 13.21                             |

## Secondary: Change from Baseline in CSF Biomarker Phosphorylated Tau

|                                                                                                                                                                                                                   |                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| End point title                                                                                                                                                                                                   | Change from Baseline in CSF Biomarker Phosphorylated Tau |
| End point description:                                                                                                                                                                                            |                                                          |
| Cerebrospinal fluid samples are collected for analysis of concentration of phosphorylated tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, baseline biomarker and age at baseline. |                                                          |
| APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CSF Phosphorylated Tau.                                                   |                                                          |
| End point type                                                                                                                                                                                                    | Secondary                                                |
| End point timeframe:                                                                                                                                                                                              |                                                          |
| Baseline, Week 71                                                                                                                                                                                                 |                                                          |



| <b>End point values</b>                | Placebo         | Lanabecestat<br>20 mg | Lanabecestat<br>50 mg |  |
|----------------------------------------|-----------------|-----------------------|-----------------------|--|
| Subject group type                     | Reporting group | Reporting group       | Reporting group       |  |
| Number of subjects analysed            | 4               | 5                     | 5                     |  |
| Units: Picogram per milliliter (pg/mL) |                 |                       |                       |  |
| least squares mean (standard error)    | 2.22 (± 1.54)   | 3.81 (± 1.49)         | 0.08 (± 1.41)         |  |

### Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | CSF Phosphorylated Tau            |
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.494                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 1.59                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -3.457                            |
| upper limit                             | 6.64                              |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 2.23                              |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | CSF Phosphorylated Tau            |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 9                                 |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.323                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -2.13                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -6.743                            |
| upper limit                             | 2.481                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 2.04                              |

### Secondary: Change From Baseline in Brain Amyloid Burden Using Florbetapir

## Amyloid Positron Emission Tomography (PET) Scan

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Brain Amyloid Burden Using Florbetapir Amyloid Positron Emission Tomography (PET) Scan |
|-----------------|----------------------------------------------------------------------------------------------------------------|

### End point description:

Amyloid deposition in the brain is one of the defining neuropathologic findings of Alzheimer's disease. Florbetapir exhibits high affinity specific binding to amyloid plaques. The change from baseline was measured as average standard uptake value ratio in prespecified regions of interest assessed by florbetapir amyloid PET imaging in a subset of participants. The Centiloid standardizes quantitative brain amyloid PET results to allow cross-tracer and cross-methodology comparisons. The Centiloid anchor points are 0 and 100, where 0 represents a high-certainty amyloid negative scan and 100 represents the amount of global amyloid deposition found in a typical AD scans. Florbetapir SUVR was converted to the Centiloid scale using the following conversion: Florbetapir Centiloids =  $183 \times \text{SUVR} - 177$ . LS Mean was determined by using ANCOVA methodology.

APD: All randomized participants who received at least one dose of study drug & have baseline and at least one post-baseline for amyloid burden.

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

### End point timeframe:

Baseline, Week 78

| End point values                    | Placebo              | Lanabecestat 20 mg  | Lanabecestat 50 mg   |  |
|-------------------------------------|----------------------|---------------------|----------------------|--|
| Subject group type                  | Reporting group      | Reporting group     | Reporting group      |  |
| Number of subjects analysed         | 7                    | 10                  | 7                    |  |
| Units: Units on a Scale             |                      |                     |                      |  |
| least squares mean (standard error) | -2.43 ( $\pm$ 10.47) | -0.21 ( $\pm$ 7.79) | -17.63 ( $\pm$ 9.69) |  |

## Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Statistical analysis title              | Florbetapir Amyloid Scan          |
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 17                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.873                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 2.22                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -26.569                           |
| upper limit                             | 31.017                            |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 13.76                             |

|                            |                          |
|----------------------------|--------------------------|
| Statistical analysis title | Florbetapir Amyloid Scan |
|----------------------------|--------------------------|

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 14                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.337                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -15.2                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -47.488                           |
| upper limit                             | 17.096                            |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 15.43                             |

### Secondary: Change from Baseline in Regional Cerebral Blood Flow (rCBF) using Florbetapir Perfusion Scan

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Change from Baseline in Regional Cerebral Blood Flow (rCBF) using Florbetapir Perfusion Scan |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                              |
| <p>Florbetapir perfusion evaluated the regional cerebral blood flow (rCBF) as a biomarker of brain function and was performed at the same time as the amyloid florbetapir PET. Cerebral perfusion, especially in temporal and parietal areas, is reduced in AD and this pattern of hypoperfusion closely mirrors the hypometabolism pattern observed using FDG PET. Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA with LOCF (last observation carried forward) and with factors for treatment, baseline biomarker and age at baseline.</p> <p>APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for rCBF.</p> |                                                                                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Secondary                                                                                    |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                              |
| Baseline, Week 78                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                              |

| End point values                          | Placebo         | Lanabecestat 20 mg | Lanabecestat 50 mg |  |
|-------------------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type                        | Reporting group | Reporting group    | Reporting group    |  |
| Number of subjects analysed               | 82              | 65                 | 66                 |  |
| Units: Standard Uptake Value ratio (SUVR) |                 |                    |                    |  |
| least squares mean (standard error)       | -0.03 (± 0.01)  | -0.03 (± 0.01)     | -0.03 (± 0.01)     |  |

### Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | rCBF                         |
| Comparison groups          | Placebo v Lanabecestat 20 mg |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 147                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.927                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 0                                 |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -0.015                            |
| upper limit                             | 0.017                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.01                              |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | rCBF                              |
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 148                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.93                            |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | 0                                 |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -0.015                            |
| upper limit                             | 0.017                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.01                              |

## Secondary: Change from Baseline in Whole Brain Volume

|                                                                                                                                                                                                                                                                                                                                                                                                            |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                            | Change from Baseline in Whole Brain Volume |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                     |                                            |
| Magnetic resonance imaging (MRI) was used to evaluate the effect of lanabecestat on brain atrophy/whole brain volumes. Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, baseline volumetric magnetic resonance imaging (vMRI), intracranial volume and age at baseline. |                                            |
| APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Whole Brain Volume.                                                                                                                                                                                                                                                |                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                             | Secondary                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                       |                                            |
| Baseline, Week 78                                                                                                                                                                                                                                                                                                                                                                                          |                                            |

| <b>End point values</b>                   | Placebo            | Lanabecestat<br>20 mg | Lanabecestat<br>50 mg |  |
|-------------------------------------------|--------------------|-----------------------|-----------------------|--|
| Subject group type                        | Reporting group    | Reporting group       | Reporting group       |  |
| Number of subjects analysed               | 215                | 215                   | 214                   |  |
| Units: cm <sup>3</sup> (cubic centimeter) |                    |                       |                       |  |
| least squares mean (standard error)       | -15.76 (±<br>0.75) | -17.38 (±<br>0.75)    | -18.84 (±<br>0.76)    |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Whole Brain Volume                |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 20 mg      |
| Number of subjects included in analysis | 430                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.127                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -1.62                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -3.708                            |
| upper limit                             | 0.464                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.06                              |

| <b>Statistical analysis title</b>       | Whole Brain Volume                |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo v Lanabecestat 50 mg      |
| Number of subjects included in analysis | 429                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.004                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | LS Mean Difference (Final Values) |
| Point estimate                          | -3.08                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -5.172                            |
| upper limit                             | -0.991                            |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 1.06                              |

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**Secondary: Population Pharmacokinetics (PK): Apparent Oral Clearance of Lanabecestat**

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|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Population Pharmacokinetics (PK): Apparent Oral Clearance of Lanabecestat |
|-----------------|---------------------------------------------------------------------------|

End point description:

The apparent oral clearance of lanabecestat was estimated using a population approach. No covariate effects were assessed as part of this analysis.

APD: All randomized participants who received at least 1 dose of study drug with evaluable PK data.

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

End point timeframe:

Predose, Week 4, 7, 19, 39, 45 and Week 71 post dose

---

|                                                     |                      |  |  |  |
|-----------------------------------------------------|----------------------|--|--|--|
| <b>End point values</b>                             | Lanabecestat         |  |  |  |
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 1077                 |  |  |  |
| Units: Liter per hour (L/h)                         |                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 17.4 ( $\pm$ 38.8)   |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Population PK: Central Volume of Distribution of Lanabecestat**

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|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Population PK: Central Volume of Distribution of Lanabecestat |
|-----------------|---------------------------------------------------------------|

End point description:

The central volume of distribution for lanabecestat was estimated using a population approach. No covariate effects were assessed as part of this analysis.

APD: All randomized participants who received at least 1 dose of study drug with evaluable PK data.

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

End point timeframe:

Predose, Week 4, 7, 19, 39, 45 and week 71 post dose

---

|                                                     |                      |  |  |  |
|-----------------------------------------------------|----------------------|--|--|--|
| <b>End point values</b>                             | Lanabecestat         |  |  |  |
| Subject group type                                  | Subject analysis set |  |  |  |
| Number of subjects analysed                         | 1077                 |  |  |  |
| Units: Liters (L)                                   |                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 77.8 ( $\pm$ 198)    |  |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up To 156 Weeks

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Lanabecestat 20 mg-Period 1 |
|-----------------------|-----------------------------|

Reporting group description:

Participants received lanabecestat 20 mg film-coated oral tablets once daily.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Lanabecestat 50 mg-Period 1 |
|-----------------------|-----------------------------|

Reporting group description:

Participants received lanabecestat 50 mg film-coated oral tablets once daily.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Placebo-Period 1 |
|-----------------------|------------------|

Reporting group description:

Participants received placebo film-coated oral tablets once daily.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Lanabecestat 20 mg-Period 2 |
|-----------------------|-----------------------------|

Reporting group description:

Participants from placebo group were randomized to receive lanabecestat 20 mg film-coated oral tablets once daily.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Lanabecestat 50 mg-Period 2 |
|-----------------------|-----------------------------|

Reporting group description:

Participants from placebo group were randomized to receive lanabecestat 50 mg film-coated oral tablets once daily.

| Serious adverse events                                              | Lanabecestat 20 mg-Period 1 | Lanabecestat 50 mg-Period 1 | Placebo-Period 1 |
|---------------------------------------------------------------------|-----------------------------|-----------------------------|------------------|
| Total subjects affected by serious adverse events                   |                             |                             |                  |
| subjects affected / exposed                                         | 50 / 588 (8.50%)            | 46 / 568 (8.10%)            | 50 / 558 (8.96%) |
| number of deaths (all causes)                                       | 2                           | 3                           | 5                |
| number of deaths resulting from adverse events                      | 1                           | 0                           | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                             |                  |
| adenocarcinoma of colon                                             |                             |                             |                  |
| alternative dictionary used: MedDRA 21.1                            |                             |                             |                  |
| subjects affected / exposed                                         | 0 / 588 (0.00%)             | 0 / 568 (0.00%)             | 1 / 558 (0.18%)  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 0                       | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0                       | 0 / 0            |
| adenocarcinoma pancreas                                             |                             |                             |                  |



|                                                    |                 |                 |                 |
|----------------------------------------------------|-----------------|-----------------|-----------------|
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| bladder transitional cell carcinoma                |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| brain neoplasm                                     |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| breast cancer                                      |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| colon cancer                                       |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| colorectal cancer                                  |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| invasive ductal breast carcinoma                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |

|                                                                         |                 |                 |                 |
|-------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                         | 0 / 0           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| lung adenocarcinoma<br>alternative dictionary used:<br>MedDRA 21.1      |                 |                 |                 |
| subjects affected / exposed                                             | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                         | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| ovarian cancer recurrent<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed <sup>[1]</sup>                              | 0 / 333 (0.00%) | 1 / 339 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all                         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| ovarian cancer stage ii<br>alternative dictionary used:<br>MedDRA 21.1  |                 |                 |                 |
| subjects affected / exposed <sup>[2]</sup>                              | 0 / 333 (0.00%) | 0 / 339 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all                         | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| pancreatic carcinoma<br>alternative dictionary used:<br>MedDRA 21.1     |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                         | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| papillary thyroid cancer<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                             | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                         | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| prostate cancer<br>alternative dictionary used:<br>MedDRA 21.1          |                 |                 |                 |
| subjects affected / exposed <sup>[3]</sup>                              | 1 / 255 (0.39%) | 0 / 229 (0.00%) | 1 / 211 (0.47%) |
| occurrences causally related to treatment / all                         | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                         |                 |                 |                 |
|---------------------------------------------------------|-----------------|-----------------|-----------------|
| renal oncocytoma                                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                             | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| squamous cell carcinoma of the<br>tongue                |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                             | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                      |                 |                 |                 |
| deep vein thrombosis                                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| hypertension                                            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| peripheral ischaemia                                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| thrombosis                                              |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration<br>site conditions |                 |                 |                 |

|                                                                                                                                |                 |                 |                 |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| chest pain<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                                       | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                                                                             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                                                                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| death<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                                            | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                                                                             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                                                                  | 0 / 0           | 0 / 0           | 0 / 1           |
| feeling abnormal<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                                 | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                                                                             | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                                                                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| non-cardiac chest pain<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                           | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                                                                             | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                                                                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| sudden cardiac death<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                             | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                                                                             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                                                                                  | 1 / 1           | 0 / 0           | 0 / 0           |
| Immune system disorders<br>anaphylactic reaction<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                                                                             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                                                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal<br>disorders<br>chronic obstructive pulmonary<br>disease                                 |                 |                 |                 |

|                                                    |                 |                 |                 |
|----------------------------------------------------|-----------------|-----------------|-----------------|
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| hiccups                                            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| hypoxia                                            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| lung disorder                                      |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| pleural effusion                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| pneumonia aspiration                               |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| pneumothorax                                       |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| pulmonary embolism                              |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| respiratory arrest                              |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Psychiatric disorders                           |                 |                 |                 |
| abnormal behaviour                              |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| acute psychosis                                 |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| adjustment disorder                             |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| aggression                                      |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| confusional state                               |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| delirium                                        |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 2 / 568 (0.35%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| delusion                                        |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| mental status changes                           |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 2 / 558 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| paranoia                                        |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| psychotic disorder                              |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                    |                 |                 |                 |
|----------------------------------------------------|-----------------|-----------------|-----------------|
| Investigations                                     |                 |                 |                 |
| prostatic specific antigen increased               |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed <sup>[4]</sup>         | 1 / 255 (0.39%) | 0 / 229 (0.00%) | 0 / 211 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural<br>complications  |                 |                 |                 |
| animal bite                                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| ankle fracture                                     |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| brain contusion                                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| clavicle fracture                                  |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| craniocerebral injury                              |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| fall                                               |                 |                 |                 |



|                                                    |                 |                 |                 |
|----------------------------------------------------|-----------------|-----------------|-----------------|
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 3 / 588 (0.51%) | 5 / 568 (0.88%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 3           | 0 / 5           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| femoral neck fracture                              |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| femur fracture                                     |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| fibula fracture                                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| forearm fracture                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| heat exhaustion                                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| hip fracture                                       |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |

|                                                                             |                 |                 |                 |
|-----------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                                                 | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                             | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| humerus fracture<br>alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                                                 | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 2 / 558 (0.36%) |
| occurrences causally related to treatment / all                             | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| lumbar vertebral fracture<br>alternative dictionary used:<br>MedDRA 21.1    |                 |                 |                 |
| subjects affected / exposed                                                 | 1 / 588 (0.17%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                             | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| pelvic fracture<br>alternative dictionary used:<br>MedDRA 21.1              |                 |                 |                 |
| subjects affected / exposed                                                 | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                             | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| post procedural complication<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                                 | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| pubis fracture<br>alternative dictionary used:<br>MedDRA 21.1               |                 |                 |                 |
| subjects affected / exposed                                                 | 0 / 588 (0.00%) | 2 / 568 (0.35%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                             | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |
| rib fracture<br>alternative dictionary used:<br>MedDRA 21.1                 |                 |                 |                 |
| subjects affected / exposed                                                 | 0 / 588 (0.00%) | 2 / 568 (0.35%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                             | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                                            |                 |                 |                 |
|----------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| road traffic accident<br>alternative dictionary used:<br>MedDRA 21.1       |                 |                 |                 |
| subjects affected / exposed                                                | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 2 / 558 (0.36%) |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 1           |
| spinal compression fracture<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                                | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| spinal fracture<br>alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                                                | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| subdural haematoma<br>alternative dictionary used:<br>MedDRA 21.1          |                 |                 |                 |
| subjects affected / exposed                                                | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| tibia fracture<br>alternative dictionary used:<br>MedDRA 21.1              |                 |                 |                 |
| subjects affected / exposed                                                | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| upper limb fracture<br>alternative dictionary used:<br>MedDRA 21.1         |                 |                 |                 |
| subjects affected / exposed                                                | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 0           |
| wrist fracture<br>alternative dictionary used:<br>MedDRA 21.1              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| gastrointestinal arteriovenous malformation     |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| acute coronary syndrome                         |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| acute myocardial infarction                     |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| atrial fibrillation                             |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 2 / 568 (0.35%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| atrial flutter                                  |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| atrioventricular block complete                 |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| cardiac arrest                                  |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| cardiac failure congestive                      |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| cardio-respiratory arrest                       |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| chronotropic incompetence                       |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| coronary artery disease                         |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| myocardial infarction                           |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |

|                                                                         |                 |                 |                 |
|-------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| sinus node dysfunction<br>alternative dictionary used:<br>MedDRA 21.1   |                 |                 |                 |
| subjects affected / exposed                                             | 2 / 588 (0.34%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                      | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| stress cardiomyopathy<br>alternative dictionary used:<br>MedDRA 21.1    |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| trifascicular block<br>alternative dictionary used:<br>MedDRA 21.1      |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| ventricular fibrillation<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                                                |                 |                 |                 |
| brain injury<br>alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| cerebellar haematoma<br>alternative dictionary used:<br>MedDRA 21.1     |                 |                 |                 |
| subjects affected / exposed                                             | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| cerebral infarction<br>alternative dictionary used:<br>MedDRA 21.1      |                 |                 |                 |

|                                                                          |                 |                 |                 |
|--------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                                              | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |
| cerebrovascular accident<br>alternative dictionary used:<br>MedDRA 21.1  |                 |                 |                 |
| subjects affected / exposed                                              | 0 / 588 (0.00%) | 2 / 568 (0.35%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                          | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |
| cognitive disorder<br>alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                                              | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                          | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |
| coma<br>alternative dictionary used:<br>MedDRA 21.1                      |                 |                 |                 |
| subjects affected / exposed                                              | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |
| dementia alzheimer's type<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                              | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                          | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |
| device malfunction<br>alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                                              | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all                          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |
| dizziness<br>alternative dictionary used:<br>MedDRA 21.1                 |                 |                 |                 |
| subjects affected / exposed                                              | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 2 / 558 (0.36%) |
| occurrences causally related to treatment / all                          | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all                               | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                                                 |                 |                 |                 |
|---------------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| encephalopathy<br>alternative dictionary used:<br>MedDRA 21.1                   |                 |                 |                 |
| subjects affected / exposed                                                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0           |
| generalised tonic-clonic seizure<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0           |
| haemorrhage intracranial<br>alternative dictionary used:<br>MedDRA 21.1         |                 |                 |                 |
| subjects affected / exposed                                                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0           |
| headache<br>alternative dictionary used:<br>MedDRA 21.1                         |                 |                 |                 |
| subjects affected / exposed                                                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0           |
| presyncope<br>alternative dictionary used:<br>MedDRA 21.1                       |                 |                 |                 |
| subjects affected / exposed                                                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                              | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0           |
| seizure<br>alternative dictionary used:<br>MedDRA 21.1                          |                 |                 |                 |
| subjects affected / exposed                                                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                              | 2 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0           |
| syncope<br>alternative dictionary used:<br>MedDRA 21.1                          |                 |                 |                 |



|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 588 (0.51%) | 3 / 568 (0.53%) | 3 / 558 (0.54%) |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| toxic encephalopathy                            |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| transient ischaemic attack                      |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| iron deficiency anaemia                         |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| vertigo positional                              |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| colitis                                         |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| colitis ischaemic                               |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| constipation                                    |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 2 / 568 (0.35%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| diverticulum                                    |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| gastrointestinal haemorrhage                    |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| inguinal hernia                                 |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| intestinal obstruction                          |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| peptic ulcer perforation                        |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                    |                 |                 |                 |
|----------------------------------------------------|-----------------|-----------------|-----------------|
| rectal prolapse                                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| vomiting                                           |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                            |                 |                 |                 |
| cholecystitis acute                                |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| cholelithiasis                                     |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                        |                 |                 |                 |
| acute kidney injury                                |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 2 / 558 (0.36%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| stress urinary incontinence                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                        | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders    |                 |                 |                 |

|                                                                         |                 |                 |                 |
|-------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| cervical spinal stenosis<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| muscle haemorrhage<br>alternative dictionary used:<br>MedDRA 21.1       |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| muscle spasms<br>alternative dictionary used:<br>MedDRA 21.1            |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| myalgia<br>alternative dictionary used:<br>MedDRA 21.1                  |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| osteoarthritis<br>alternative dictionary used:<br>MedDRA 21.1           |                 |                 |                 |
| subjects affected / exposed                                             | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                                             |                 |                 |                 |
| bacteraemia<br>alternative dictionary used:<br>MedDRA 21.1              |                 |                 |                 |
| subjects affected / exposed                                             | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| bronchitis viral<br>alternative dictionary used:<br>MedDRA 21.1         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| cellulitis                                      |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| cellulitis orbital                              |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 588 (0.00%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| epididymitis                                    |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed <sup>[5]</sup>      | 1 / 255 (0.39%) | 0 / 229 (0.00%) | 1 / 211 (0.47%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| erysipelas                                      |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| liver abscess                                   |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 588 (0.17%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| orchitis                                        |                 |                 |                 |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                 |
| subjects affected / exposed <sup>[6]</sup>      | 0 / 255 (0.00%) | 0 / 229 (0.00%) | 1 / 211 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                                        |                 |                 |                 |
|------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| pneumonia<br>alternative dictionary used:<br>MedDRA 21.1               |                 |                 |                 |
| subjects affected / exposed                                            | 1 / 588 (0.17%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                     | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           | 0 / 1           |
| sepsis<br>alternative dictionary used:<br>MedDRA 21.1                  |                 |                 |                 |
| subjects affected / exposed                                            | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 1           | 0 / 0           |
| sinusitis<br>alternative dictionary used:<br>MedDRA 21.1               |                 |                 |                 |
| subjects affected / exposed                                            | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| urinary tract infection<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                            | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                     | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| urosepsis<br>alternative dictionary used:<br>MedDRA 21.1               |                 |                 |                 |
| subjects affected / exposed                                            | 0 / 588 (0.00%) | 1 / 568 (0.18%) | 1 / 558 (0.18%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders                                     |                 |                 |                 |
| decreased appetite<br>alternative dictionary used:<br>MedDRA 21.1      |                 |                 |                 |
| subjects affected / exposed                                            | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to<br>treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| dehydration<br>alternative dictionary used:<br>MedDRA 21.1             |                 |                 |                 |

|                                                              |                 |                 |                 |
|--------------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                                  | 2 / 588 (0.34%) | 1 / 568 (0.18%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all              | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0           |
| hypoglycaemia<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                  | 1 / 588 (0.17%) | 0 / 568 (0.00%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all              | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0           |
| hyponatraemia<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                 |
| subjects affected / exposed                                  | 0 / 588 (0.00%) | 2 / 568 (0.35%) | 0 / 558 (0.00%) |
| occurrences causally related to treatment / all              | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                                                                                                                 | Lanabecestat 20 mg-Period 2 | Lanabecestat 50 mg-Period 2 |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events                                                                                             |                             |                             |  |
| subjects affected / exposed                                                                                                                   | 0 / 14 (0.00%)              | 1 / 12 (8.33%)              |  |
| number of deaths (all causes)                                                                                                                 | 0                           | 0                           |  |
| number of deaths resulting from adverse events                                                                                                | 0                           | 0                           |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>adenocarcinoma of colon<br>alternative dictionary used:<br>MedDRA 21.1 |                             |                             |  |
| subjects affected / exposed                                                                                                                   | 0 / 14 (0.00%)              | 0 / 12 (0.00%)              |  |
| occurrences causally related to treatment / all                                                                                               | 0 / 0                       | 0 / 0                       |  |
| deaths causally related to treatment / all                                                                                                    | 0 / 0                       | 0 / 0                       |  |
| adenocarcinoma pancreas<br>alternative dictionary used:<br>MedDRA 21.1                                                                        |                             |                             |  |
| subjects affected / exposed                                                                                                                   | 0 / 14 (0.00%)              | 0 / 12 (0.00%)              |  |
| occurrences causally related to treatment / all                                                                                               | 0 / 0                       | 0 / 0                       |  |
| deaths causally related to treatment / all                                                                                                    | 0 / 0                       | 0 / 0                       |  |
| bladder transitional cell carcinoma<br>alternative dictionary used:<br>MedDRA 21.1                                                            |                             |                             |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| brain neoplasm                                  |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| breast cancer                                   |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| colon cancer                                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| colorectal cancer                               |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| invasive ductal breast carcinoma                |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| lung adenocarcinoma                             |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |



|                                                                                                                       |                |                |  |  |
|-----------------------------------------------------------------------------------------------------------------------|----------------|----------------|--|--|
| ovarian cancer recurrent<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[1]</sup> | 0 / 9 (0.00%)  | 0 / 5 (0.00%)  |  |  |
| occurrences causally related to<br>treatment / all                                                                    | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                         | 0 / 0          | 0 / 0          |  |  |
| ovarian cancer stage ii<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[2]</sup>  | 0 / 9 (0.00%)  | 0 / 5 (0.00%)  |  |  |
| occurrences causally related to<br>treatment / all                                                                    | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                         | 0 / 0          | 0 / 0          |  |  |
| pancreatic carcinoma<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                    | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                                    | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                         | 0 / 0          | 0 / 0          |  |  |
| papillary thyroid cancer<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                                    | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                         | 0 / 0          | 0 / 0          |  |  |
| prostate cancer<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[3]</sup>          | 0 / 5 (0.00%)  | 0 / 7 (0.00%)  |  |  |
| occurrences causally related to<br>treatment / all                                                                    | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                         | 0 / 0          | 0 / 0          |  |  |
| renal oncocytoma<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                                    | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                         | 0 / 0          | 0 / 0          |  |  |
| squamous cell carcinoma of the<br>tongue<br>alternative dictionary used:<br>MedDRA 21.1                               |                |                |  |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Vascular disorders                                   |                |                |  |
| deep vein thrombosis                                 |                |                |  |
| alternative dictionary used: MedDRA 21.1             |                |                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| hypertension                                         |                |                |  |
| alternative dictionary used: MedDRA 21.1             |                |                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| peripheral ischaemia                                 |                |                |  |
| alternative dictionary used: MedDRA 21.1             |                |                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| thrombosis                                           |                |                |  |
| alternative dictionary used: MedDRA 21.1             |                |                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| chest pain                                           |                |                |  |
| alternative dictionary used: MedDRA 21.1             |                |                |  |
| subjects affected / exposed                          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| death                                                |                |                |  |
| alternative dictionary used: MedDRA 21.1             |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| feeling abnormal                                |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| non-cardiac chest pain                          |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| sudden cardiac death                            |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune system disorders                         |                |                |  |
| anaphylactic reaction                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| chronic obstructive pulmonary disease           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| hiccups                                         |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| hypoxia                                         |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| lung disorder                                   |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pleural effusion                                |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pneumonia aspiration                            |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pneumothorax                                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pulmonary embolism                              |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                                                                   |                |                |  |
|---------------------------------------------------------------------------------------------------|----------------|----------------|--|
| respiratory arrest<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed  | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                                | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                                                     | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                                                                             |                |                |  |
| abnormal behaviour<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed  | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                                | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                                                     | 0 / 0          | 0 / 0          |  |
| acute psychosis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                                | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                                                     | 0 / 0          | 0 / 0          |  |
| adjustment disorder<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                                | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                                                     | 0 / 0          | 0 / 0          |  |
| aggression<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed          | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                                | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                                                     | 0 / 0          | 0 / 0          |  |
| confusional state<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed   | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                                | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                                                     | 0 / 0          | 0 / 0          |  |
| delirium<br>alternative dictionary used:<br>MedDRA 21.1                                           |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| delusion                                        |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| mental status changes                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| paranoia                                        |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| psychotic disorder                              |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| prostatic specific antigen increased            |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed <sup>[4]</sup>      | 0 / 5 (0.00%)  | 0 / 7 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| animal bite                                     |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ankle fracture                                  |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| brain contusion                                 |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| clavicle fracture                               |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| craniocerebral injury                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| fall                                            |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| femoral neck fracture                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                    |                |                |  |  |
|----------------------------------------------------|----------------|----------------|--|--|
| femur fracture                                     |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| fibula fracture                                    |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| forearm fracture                                   |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| heat exhaustion                                    |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| hip fracture                                       |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| humerus fracture                                   |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| lumbar vertebral fracture                          |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |



|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pelvic fracture                                 |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| post procedural complication                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pubis fracture                                  |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| rib fracture                                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| road traffic accident                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| spinal compression fracture                     |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                    |                |                |  |
|----------------------------------------------------|----------------|----------------|--|
| spinal fracture                                    |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| subdural haematoma                                 |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| tibia fracture                                     |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| upper limb fracture                                |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| wrist fracture                                     |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| Congenital, familial and genetic disorders         |                |                |  |
| gastrointestinal arteriovenous malformation        |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                                  |                |                |  |

|                                                                                                               |                |                |  |  |
|---------------------------------------------------------------------------------------------------------------|----------------|----------------|--|--|
| acute coronary syndrome<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed         | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                            | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                 | 0 / 0          | 0 / 0          |  |  |
| acute myocardial infarction<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                            | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                 | 0 / 0          | 0 / 0          |  |  |
| atrial fibrillation<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed             | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                            | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                 | 0 / 0          | 0 / 0          |  |  |
| atrial flutter<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                  | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                            | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                 | 0 / 0          | 0 / 0          |  |  |
| atrioventricular block complete<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                            | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                 | 0 / 0          | 0 / 0          |  |  |
| cardiac arrest<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed                  | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                                                            | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                                                                 | 0 / 0          | 0 / 0          |  |  |
| cardiac failure congestive<br>alternative dictionary used:<br>MedDRA 21.1                                     |                |                |  |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| cardio-respiratory arrest                       |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| chronotropic incompetence                       |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| coronary artery disease                         |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| myocardial infarction                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| sinus node dysfunction                          |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| stress cardiomyopathy                           |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                    |                |                |  |
|----------------------------------------------------|----------------|----------------|--|
| trifascicular block                                |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| ventricular fibrillation                           |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                           |                |                |  |
| brain injury                                       |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cerebellar haematoma                               |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cerebral infarction                                |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cerebrovascular accident                           |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cognitive disorder                                 |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |

|                                                 |                |                |  |  |
|-------------------------------------------------|----------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |
| coma                                            |                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |
| dementia alzheimer's type                       |                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |
| device malfunction                              |                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |
| dizziness                                       |                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |
| encephalopathy                                  |                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |
| generalised tonic-clonic seizure                |                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |  |

|                                                    |                |                |  |  |
|----------------------------------------------------|----------------|----------------|--|--|
| haemorrhage intracranial                           |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| headache                                           |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| presyncope                                         |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| seizure                                            |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| syncope                                            |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| toxic encephalopathy                               |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |  |
| transient ischaemic attack                         |                |                |  |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| iron deficiency anaemia                         |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ear and labyrinth disorders                     |                |                |  |
| vertigo positional                              |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| colitis                                         |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| colitis ischaemic                               |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| constipation                                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| diverticulum                                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |



|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| gastrointestinal haemorrhage                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| inguinal hernia                                 |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| intestinal obstruction                          |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| peptic ulcer perforation                        |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| rectal prolapse                                 |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| vomiting                                        |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                    |                |                |  |
|----------------------------------------------------|----------------|----------------|--|
| Hepatobiliary disorders                            |                |                |  |
| cholecystitis acute                                |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cholelithiasis                                     |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                        |                |                |  |
| acute kidney injury                                |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| stress urinary incontinence                        |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders    |                |                |  |
| cervical spinal stenosis                           |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| muscle haemorrhage                                 |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| muscle spasms                                      |                |                |  |

|                                                    |                |                |  |
|----------------------------------------------------|----------------|----------------|--|
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| myalgia                                            |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| osteoarthritis                                     |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                        |                |                |  |
| bacteraemia                                        |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| bronchitis viral                                   |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cellulitis                                         |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |
| subjects affected / exposed                        | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          |  |
| cellulitis orbital                                 |                |                |  |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| epididymitis                                    |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed <sup>[5]</sup>      | 0 / 5 (0.00%)  | 0 / 7 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| erysipelas                                      |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| liver abscess                                   |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| orchitis                                        |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed <sup>[6]</sup>      | 0 / 5 (0.00%)  | 0 / 7 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| pneumonia                                       |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| sepsis                                          |                |                |  |
| alternative dictionary used: MedDRA 21.1        |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                                                                                                                                                                                                               |                                  |                                  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|--|
| sinusitis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                | 0 / 14 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| urinary tract infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                  | 0 / 14 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| urosepsis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                | 0 / 14 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Metabolism and nutrition disorders<br>decreased appetite<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 14 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| dehydration<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                              | 0 / 14 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| hypoglycaemia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                            | 0 / 14 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| hyponatraemia<br>alternative dictionary used:<br>MedDRA 21.1                                                                                                                                                                                  |                                  |                                  |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

| <b>Non-serious adverse events</b>                     | Lanabecestat 20 mg-Period 1 | Lanabecestat 50 mg-Period 1 | Placebo-Period 1 |
|-------------------------------------------------------|-----------------------------|-----------------------------|------------------|
| Total subjects affected by non-serious adverse events |                             |                             |                  |
| subjects affected / exposed                           | 69 / 588 (11.73%)           | 76 / 568 (13.38%)           | 48 / 558 (8.60%) |
| Investigations                                        |                             |                             |                  |
| blood glucose decreased                               |                             |                             |                  |
| alternative dictionary used: MedDRA 21.1              |                             |                             |                  |
| subjects affected / exposed                           | 0 / 588 (0.00%)             | 0 / 568 (0.00%)             | 0 / 558 (0.00%)  |
| occurrences (all)                                     | 0                           | 0                           | 0                |
| thyroxine decreased                                   |                             |                             |                  |
| alternative dictionary used: MedDRA 21.1              |                             |                             |                  |
| subjects affected / exposed                           | 0 / 588 (0.00%)             | 2 / 568 (0.35%)             | 0 / 558 (0.00%)  |
| occurrences (all)                                     | 0                           | 2                           | 0                |
| Injury, poisoning and procedural complications        |                             |                             |                  |
| fall                                                  |                             |                             |                  |
| alternative dictionary used: MedDRA 21.1              |                             |                             |                  |
| subjects affected / exposed                           | 32 / 588 (5.44%)            | 34 / 568 (5.99%)            | 21 / 558 (3.76%) |
| occurrences (all)                                     | 37                          | 49                          | 34               |

|                                                                                                                                                                                                                                                                      |                                                  |                                                  |                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| General disorders and administration site conditions<br>influenza like illness<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                                                                       | 1 / 588 (0.17%)<br>1                             | 4 / 568 (0.70%)<br>4                             | 1 / 558 (0.18%)<br>1                             |
| Eye disorders<br>glaucoma<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                            | 4 / 588 (0.68%)<br>4                             | 3 / 568 (0.53%)<br>3                             | 5 / 558 (0.90%)<br>5                             |
| Reproductive system and breast disorders<br>benign prostatic hyperplasia<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed <sup>[7]</sup><br>occurrences (all)                                                                              | 4 / 255 (1.57%)<br>4                             | 3 / 229 (1.31%)<br>3                             | 4 / 211 (1.90%)<br>4                             |
| Gastrointestinal disorders<br>diarrhoea<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                                                                                                              | 29 / 588 (4.93%)<br>35                           | 29 / 568 (5.11%)<br>39                           | 17 / 558 (3.05%)<br>19                           |
| Psychiatric disorders<br>confusional state<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)<br><br>psychotic disorder<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 4 / 588 (0.68%)<br>4<br><br>1 / 588 (0.17%)<br>1 | 9 / 568 (1.58%)<br>9<br><br>0 / 568 (0.00%)<br>0 | 2 / 558 (0.36%)<br>2<br><br>0 / 558 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>hyperlipidaemia<br>alternative dictionary used: MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                                                                                                | 1 / 588 (0.17%)<br>1                             | 1 / 568 (0.18%)<br>1                             | 1 / 558 (0.18%)<br>1                             |

|                                   |                             |                             |  |
|-----------------------------------|-----------------------------|-----------------------------|--|
| <b>Non-serious adverse events</b> | Lanabecestat 20 mg-Period 2 | Lanabecestat 50 mg-Period 2 |  |
|-----------------------------------|-----------------------------|-----------------------------|--|

|                                                                                                                                                                                            |                     |                     |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                                       | 5 / 14 (35.71%)     | 1 / 12 (8.33%)      |  |
| Investigations<br>blood glucose decreased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 |  |
| thyroxine decreased<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                                                     | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 |  |
| Injury, poisoning and procedural complications<br>fall<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 14 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| General disorders and administration site conditions<br>influenza like illness<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)          | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 |  |
| Eye disorders<br>glaucoma<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                                               | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 |  |
| Reproductive system and breast disorders<br>benign prostatic hyperplasia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[7]</sup><br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 7 (0.00%)<br>0  |  |
| Gastrointestinal disorders<br>diarrhoea<br>alternative dictionary used:<br>MedDRA 21.1                                                                                                     |                     |                     |  |



|                                                                                                                                                          |                     |                     |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                         | 0 / 14 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Psychiatric disorders<br>confusional state<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)            | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 |  |
| psychotic disorder<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 14 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 |  |
| Metabolism and nutrition disorders<br>hyperlipidaemia<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 |  |

Notes:

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------|
| An independent assessment concluded the trial was not likely to meet the primary endpoint upon completion and therefore, trial stopped for futility. |
|------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes: