# Clinical trial results:
# A 24-Month, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy, Safety, Tolerability, Biomarker and Pharmacokinetics Study of AZD3293 in Early Alzheimer's Disease (The AMARANTH Study)

## Summary

| | |
|---|---|
| EudraCT number | 2014-002601-38 |
| Trial protocol | GB BE DE ES HU FR IT |
| Global end of trial date | 04 October 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-AZES |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02245737 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 16023 |

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 | 04 October 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 04 October 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of lanabecestat compared with placebo administered for 104 weeks in the treatment of early Alzheimer´s disease. The study will test the hypothesis that lanabecestat is a disease-modifying treatment for participants with early Alzheimer´s disease, defined as the continuum of participants with mild cognitive impairment (MCI) due to Alzheimer´s disease and participants diagnosed with mild dementia of the Alzheimer´s type, as measured by change from baseline on the 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13) score at week 104 in each of the 2 lanabecestat treatment groups compared with placebo.

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 | 30 September 2014 |
| 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 | Romania: 5 |
| Country: Number of subjects enrolled | Puerto Rico: 36 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Country: Number of subjects enrolled | United States: 521 |
| Country: Number of subjects enrolled | Japan: 183 |
| Country: Number of subjects enrolled | United Kingdom: 250 |
| Country: Number of subjects enrolled | Spain: 216 |
| Country: Number of subjects enrolled | Canada: 180 |
| Country: Number of subjects enrolled | Korea, Republic of: 70 |
| Country: Number of subjects enrolled | Belgium: 50 |

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 159 |
| Country: Number of subjects enrolled | Italy: 132 |
| Country: Number of subjects enrolled | Australia: 131 |
| Country: Number of subjects enrolled | France: 117 |
| Country: Number of subjects enrolled | Germany: 143 |
| Worldwide total number of subjects | 2218 |
| EEA total number of subjects | 1097 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 423 |
| From 65 to 84 years | 1770 |
| 85 years and over | 25 |

## Subject disposition

### Recruitment

Recruitment details:

No Text Available

### Pre-assignment

Screening details:

No Text Available

### Period 1

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

### Arms

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

| | |
|---|---|
| **Arm title** | 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.

| | |
|---|---|
| **Arm title** | 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.

| **Number of subjects in period 1** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg |
|---|---|---|---|
| Started | 740 | 739 | 739 |
| Received at least 1 Dose of Study drug | 738 | 736 | 735 |
| Completed | 187 | 184 | 168 |
| Not completed | 553 | 555 | 571 |
| Adverse event, serious fatal | 2 | 4 | 4 |
| Condition Worsened | 9 | 10 | 9 |
| Physician decision | 6 | 3 | 6 |
| Consent withdrawn by subject | 40 | 41 | 44 |
| Eligibility Criteria No Longer Met | 2 | 4 | 4 |
| Adverse event, non-fatal | 23 | 26 | 33 |
| Withdrawal due to Caregiver Circumstance | 10 | 20 | 22 |
| Sponsor Decision | 445 | 430 | 432 |
| Lost to follow-up | 2 | 5 | 4 |
| Other Selected by Investigator | 9 | 10 | 10 |
| Initiation of Symptomatic AD medication | 2 | - | - |
| Protocol deviation | 3 | 2 | 3 |

## 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 | 740 | 739 | 739 |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | 71.4 | 71.2 | 71.2 |
| standard deviation | ± 6.9 | ± 7.5 | ± 7.0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 398 | 395 | 384 |
| Male | 342 | 344 | 355 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 43 | 26 | 24 |
| Not Hispanic or Latino | 626 | 650 | 644 |
| Unknown or Not Reported | 71 | 63 | 71 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 85 | 85 | 102 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 5 | 5 | 6 |
| White | 598 | 609 | 593 |
| More than one race | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Unknown or Not Reported | 52 | 40 | 38 |
| Region of Enrollment<br>Units: Subjects | | | |
| Puerto Rico | 13 | 11 | 12 |
| Romania | 1 | 2 | 2 |
| Hungary | 7 | 12 | 6 |
| United States | 171 | 171 | 179 |
| Japan | 48 | 57 | 78 |
| United Kingdom | 85 | 87 | 78 |
| Spain | 74 | 77 | 65 |
| Canada | 58 | 59 | 63 |
| South Korea | 30 | 24 | 16 |
| Belgium | 20 | 15 | 15 |
| Poland | 58 | 51 | 50 |
| Italy | 45 | 38 | 49 |
| Australia | 38 | 55 | 38 |
| France | 45 | 36 | 36 |
| Germany | 47 | 44 | 52 |
| 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 | 28.6 | 29.0 | 28.5 |
| standard deviation | ± 7.9 | ± 7.7 | ± 8.2 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 2218 | | |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1177 | | |
| Male | 1041 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 93 | | |

| | | | |
|---|---|---|---|
| Not Hispanic or Latino | 1920 | | |
| Unknown or Not Reported | 205 | | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 272 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 16 | | |
| White | 1800 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 130 | | |
| Region of Enrollment<br>Units: Subjects | | | |
| Puerto Rico | 36 | | |
| Romania | 5 | | |
| Hungary | 25 | | |
| United States | 521 | | |
| Japan | 183 | | |
| United Kingdom | 250 | | |
| Spain | 216 | | |
| Canada | 180 | | |
| South Korea | 70 | | |
| Belgium | 50 | | |
| Poland | 159 | | |
| Italy | 132 | | |
| Australia | 131 | | |
| France | 117 | | |
| Germany | 143 | | |
| 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<br>arithmetic mean<br>standard deviation | -<br> | | |

## 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. | |

### Primary: Change from Baseline on the 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13)

| | |
|---|---|
| End point title | Change from Baseline on the 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13) |

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, disease status at baseline, apolipoprotein E4 (APOE4) status, acetylcholinesterase inhibitor (AChEI) use at baseline, pooled country, and covariates for baseline ADAS-Cog13 total score-by-visit interaction. Analysis Population Description: 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 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 723 | 722 | 708 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 10.31 (± 0.55) | 9.38 (± 0.56) | 10.72 (± 0.58) | |

### Statistical analyses

| Statistical analysis title | ADAS-Cog13 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |

| | |
|---|---|
| Number of subjects included in analysis | 1445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.232 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.447 |
| upper limit | 0.594 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.77 |

| **Statistical analysis title** | ADAS-Cog13 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.599 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.124 |
| upper limit | 1.947 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.78 |

## Secondary: Change from Baseline on the Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items (ADCS-iADL)

| End point title | Change from Baseline on the Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items (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, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, and covariates for baseline 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 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 702 | 700 | 674 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -8.87 (± 0.60) | -8.84 (± 0.61) | -8.79 (± 0.63) | |

**Statistical analyses**

| Statistical analysis title | ADCS-iADL |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1402 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.971 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.609 |
| upper limit | 1.669 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.83 |

| Statistical analysis title | ADCS-iADL |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1376 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.923 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.58 |
| upper limit | 1.743 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.85 |

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

| End point title | Change from Baseline on the 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 was calculated by MMRM.
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 104

| **End point values** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 699 | 697 | 674 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 6.09 (± 0.38) | 5.96 (± 0.39) | 6.71 (± 0.40) | |

### Statistical analyses

| **Statistical analysis title** | FAQ Score |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1396 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.796 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.172 |
| upper limit | 0.899 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.53 |

| Statistical analysis title | FAQ Score |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1373 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.252 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.437 |
| upper limit | 1.66 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.53 |

## 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 form 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 with higher scores indicating greater impairment. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, 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 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 696 | 689 | 662 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -19.56 (± 0.99) | -18.45 (± 1.02) | -19.69 (± 1.05) | |

**Statistical analyses**

| **Statistical analysis title** | iADRS |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1385 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.428 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.637 |
| upper limit | 3.852 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.4 |

| **Statistical analysis title** | iADRS |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.926 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.918 |
| upper limit | 2.655 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.42 |

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

| End point title | Change from Baseline on 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 of the following 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, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, 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 104

| **End point values** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 704 | 705 | 676 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 3.02 (± 0.17) | 3.17 (± 0.17) | 3.17 (± 0.18) | |

**Statistical analyses**

| **Statistical analysis title** | CDR-SB |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1409 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.533 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.322 |
| upper limit | 0.622 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

| **Statistical analysis title** | CDR-SB |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1380 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.537 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.15 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.328 |
| upper limit | 0.63 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

## 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:

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).
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.

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

End point timeframe:

Baseline through Loss of 1 Global Stage or Week 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 716 | 714 | 696 | |
| Units: Days | | | | |
| median (confidence interval 95%) | 548 (547 to 554) | 547 (545 to 550) | 548 (545 to 553) | |

### Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Change from Baseline in Neuropsychiatric Inventory (NPI) Score |

End point description:

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 indicated a greater severity of neuropsychiatric disturbance. LS Mean was determined by MMRM methodology.
APD: All randomized participants who received at least one dose of study drug and have baseline and at

least one post-baseline data for NPI.

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: Baseline, Week 104 | |

| **End point values** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 697 | 695 | 663 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 3.22 (± 0.81) | 4.99 (± 0.83) | 4.67 (± 0.85) | |

**Statistical analyses**

| **Statistical analysis title** | NPI |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1392 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.116 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 1.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.441 |
| upper limit | 3.986 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.13 |

| **Statistical analysis title** | NPI |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1360 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.208 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 1.45 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.808 |
| upper limit | 3.704 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.15 |

## 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 higher score indicating better cognitive performance. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, 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 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 723 | 725 | 709 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -5.50 (± 0.26) | -5.18 (± 0.26) | -5.49 (± 0.27) | |

### Statistical analyses

| Statistical analysis title | MMSE |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1448 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.379 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.32 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.391 |
| upper limit | 1.027 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.36 |

| **Statistical analysis title** | MMSE |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 1432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.992 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.714 |
| upper limit | 0.721 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.37 |

## Secondary: Pharmacodynamics (PD): Percent Change from Baseline in Concentration of Cerebrospinal Fluid (CSF) Biomarker Aβ1-42

| End point title | Pharmacodynamics (PD): Percent Change from Baseline in Concentration of Cerebrospinal Fluid (CSF) Biomarker Aβ1-42 |
|---|---|

End point description:

Concentration of the peptide Aβ 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.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Aβ1-42.

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

End point timeframe:

Baseline, Week 97

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 63 | 66 | 79 | |
| Units: Percentage change in Aβ1-42 | | | | |
| least squares mean (standard error) | -2.64 (± 2.07) | -53.91 (± 2.04) | -68.13 (± 1.87) | |

**Statistical analyses**

| Statistical analysis title | Aβ1-42 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 129 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -51.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -56.963 |
| upper limit | -45.578 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.89 |

| Statistical analysis title | Aβ1-42 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -65.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -70.947 |
| upper limit | -60.022 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.77 |

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

| End point title | PD: Change from Baseline in Concentration of CSF Biomarker Aβ1-40 |
|---|---|

End point description:

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.
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:

Baseline, Week 97

| **End point values** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 64 | 66 | 79 | |
| Units: Percentage change in Aβ1-40 | | | | |
| least squares mean (standard error) | -1.92 (± 1.77) | -59.90 (± 1.74) | -75.17 (± 1.60) | |

**Statistical analyses**

| **Statistical analysis title** | Aβ1-40 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -57.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -62.865 |
| upper limit | -53.108 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.47 |

| **Statistical analysis title** | Aβ1-40 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -73.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -77.926 |
| upper limit | -68.575 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.37 |

## Secondary: Change from Baseline in CSF Total Tau

| | |
|---|---|
| End point title | Change from Baseline in CSF Total Tau |

End point description:

Cerebrospinal fluid samples are collected for analysis of concentration total tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, disease status at baseline, 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 97

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 64 | 66 | 79 | |
| Units: Picogram per milliliter (pg/mL) | | | | |
| least squares mean (standard error) | 12.39 (± 8.05) | -7.48 (± 8.01) | -2.92 (± 7.30) | |

### Statistical analyses

| Statistical analysis title | CSF Total Tau |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.081 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -19.87 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42.21 |
| upper limit | 2.464 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 11.33 |

| | |
|---|---|
| **Statistical analysis title** | CSF Total Tau |
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.157 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -15.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.555 |
| upper limit | 5.938 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 10.78 |

**Secondary: Change from Baseline in CSF Phosphorylated Tau**

| | |
|---|---|
| End point title | Change from Baseline in CSF Phosphorylated Tau |

End point description:

Cerebrospinal fluid samples are collected for analysis of concentrations of phosphorylated tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, disease status at baseline, 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 97

| **End point values** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 63 | 66 | 79 | |
| Units: Picogram per milliliter (pg/mL) | | | | |
| least squares mean (standard error) | 0.47 (± 0.95) | -2.16 (± 0.94) | -1.66 (± 0.85) | |

**Statistical analyses**

| **Statistical analysis title** | CSF Phosphorylated Tau |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 129 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -2.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.243 |
| upper limit | -0.002 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.33 |

| **Statistical analysis title** | CSF Phosphorylated Tau |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -2.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.618 |
| upper limit | 0.373 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.27 |

## 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 (SUVr) in prespecified ROI assessed by florbetapir amyloid PET imaging in a subset of participants. The Centiloid scale standardizes quantitative brain amyloid PET results to allow cross-tracer and cross-methodology comparisons. The Centiloid scale 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 x SUVr - 177 LS Mean was determined by ANCOVA .
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for brain amyloid burden.

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

End point timeframe:

Baseline, Week 104

| **End point values** | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 133 | 127 | 116 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -2.08 (± 1.86) | -15.76 (± 1.89) | -19.74 (± 1.97) | |

**Statistical analyses**

| **Statistical analysis title** | Florbetapir Amyloid Scan |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 260 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -13.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.785 |
| upper limit | -8.574 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.6 |

| **Statistical analysis title** | Florbetapir Amyloid Scan |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 249 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -17.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.887 |
| upper limit | -12.428 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.66 |

## Secondary: Change From Baseline in Tau PET (Flortaucipir F18)

| | |
|---|---|
| End point title | Change From Baseline in Tau PET (Flortaucipir F18) |

End point description:

Tau PET tracer (flortaucipir F18) longitudinal study measured whether lanabecestat, in patients with mild AD dementia, affected tau density and distribution over time. It was planned that up to 4 scans would be performed over 3 years at sites with access to flortaucipir F 18. The outcome reported is the composite summary of SUVRs normalized to the signal intensity in white matter. Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA methodology with factors for treatment, disease status at baseline, baseline biomarker and age at baseline. Baseline defined to be within 28 days of starting study drug.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Tau PET.

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

End point timeframe:

Baseline, Week 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 97 | 94 | 93 | |
| Units: Standard Uptake Value ratio (SUVr) | | | | |
| least squares mean (standard error) | 0.04 (± 0.01) | 0.03 (± 0.01) | 0.03 (± 0.01) | |

### Statistical analyses

| Statistical analysis title | Flortaucipir F18 |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |

| | |
|---|---|
| Number of subjects included in analysis | 191 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.426 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.033 |
| upper limit | 0.014 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.01 |

| | |
|---|---|
| **Statistical analysis title** | Flortaucipir F18 |
| Comparison groups | Placebo v Lanabecestat 50 mg |
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.66 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.029 |
| upper limit | 0.018 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.01 |

## Secondary: Change From Baseline in Brain Metabolism Using Fluorodeoxyglucose (FDG)

| | |
|---|---|
| End point title | Change From Baseline in Brain Metabolism Using Fluorodeoxyglucose (FDG) |

End point description:

Fluorodeoxyglucose (FDG) PET evaluates the regional brain metabolic rates for glucose as a sensitive, in vivo metabolic index of brain function. The outcome reported is the composite summary of the standard uptake value ratio (SUVR) normalized to the pons + vermis assessed with composite meta and composite meta automated anatomical labeling atlas (ALL). Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA methodology with factors for treatment, disease status at baseline, baseline biomarker and age at baseline. Baseline defined to be within 28 days of starting study drug.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data of brain metabolism.

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

End point timeframe:

Baseline, Week 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 95 | 82 | |
| Units: Standard Uptake Value ratio (SUVr) | | | | |
| least squares mean (standard error) | -0.04 (± 0.00) | -0.05 (± 0.00) | -0.05 (± 0.00) | |

**Statistical analyses**

| Statistical analysis title | FDG |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.21 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.015 |
| upper limit | 0.003 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0 |

| Statistical analysis title | FDG |
|---|---|
| Comparison groups | Lanabecestat 50 mg v Placebo |
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.568 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.013 |
| upper limit | 0.007 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0 |

## 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 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 methodology with factors for treatment, baseline vMRI, intracranial volume, disease status at baseline 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 104

| End point values | Placebo | Lanabecestat 20 mg | Lanabecestat 50 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 565 | 582 | 550 | |
| Units: cm^3 (cubic centimeter) | | | | |
| least squares mean (standard error) | -14.16 (± 0.34) | -16.49 (± 0.33) | -17.34 (± 0.34) | |

### Statistical analyses

| Statistical analysis title | Whole Brain Volume |
|---|---|
| Comparison groups | Placebo v Lanabecestat 20 mg |
| Number of subjects included in analysis | 1147 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.258 |
| upper limit | -1.413 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.47 |

| Statistical analysis title | Whole Brain Volume |
|---|---|
| Comparison groups | Placebo v Lanabecestat 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 1115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -3.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.118 |
| upper limit | -2.247 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.48 |

## Secondary: Pharmacokinetics (PK): Plasma Concentration of Lanabecestat

| | |
|---|---|
| End point title | Pharmacokinetics (PK): Plasma Concentration of |

End point description:

Plasma Concentration of Lanabecestat.
APD: All randomized participants who received at least one dose of study drug and have evaluable PK data.

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

End point timeframe:

Week 4, post dose prior to departure from the clinic

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No arm comparison analyses were planned or conducted.

| End point values | Lanabecestat 20 mg | Lanabecestat 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 697 | 662 | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | 67.7 (± 49.1) | 213 (± 149) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up To 104 weeks

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. There are gender specific adverse events, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

| | |
|---|---|
| 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 | Placebo |

Reporting group description:

Participants received placebo film-coated oral tablets once daily.

| Serious adverse events | Lanabecestat 20 mg | Lanabecestat 50 mg | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 117 / 736 (15.90%) | 147 / 735 (20.00%) | 108 / 738 (14.63%) |
| number of deaths (all causes) | 4 | 4 | 2 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| acoustic neuroma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| acute myeloid leukaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| adenocarcinoma of colon | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| basal cell carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| bile duct adenocarcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| bladder neoplasm | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| breast cancer male | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed[1] | 1 / 344 (0.29%) | 0 / 354 (0.00%) | 0 / 341 (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 |
| breast cancer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| breast cancer recurrent | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| colon cancer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| endometrial adenocarcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed[2] | 0 / 392 (0.00%) | 0 / 381 (0.00%) | 1 / 397 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| haemangioma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| invasive ductal breast carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| laryngeal squamous cell carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| lentigo maligna | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| lung adenocarcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 3 / 735 (0.41%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lung neoplasm | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lymphoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| lung neoplasm malignant | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| malignant melanoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| malignant melanoma in situ | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| malignant neoplasm of unknown primary site | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| metastases to bone | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| metastases to lymph nodes | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| neuroendocrine tumour | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ovarian adenoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed[3] | 0 / 392 (0.00%) | 1 / 381 (0.26%) | 0 / 397 (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 |
| pancreatic carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| prostate cancer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed[4] | 2 / 344 (0.58%) | 2 / 354 (0.56%) | 2 / 341 (0.59%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| prostatic adenoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed[5] | 0 / 344 (0.00%) | 0 / 354 (0.00%) | 1 / 341 (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 |
| rectal adenoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 adenocarcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| rectal cancer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| small cell lung cancer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| squamous cell carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| transitional cell carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| aortic aneurysm | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| deep vein thrombosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| granulomatosis with polyangiitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| haematoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| hypertension | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| hypertensive crisis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hypotension | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| orthostatic hypotension | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| peripheral artery stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| temporal arteritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| thrombophlebitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| venous thrombosis limb | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| Surgical and medical procedures | | | |
| cardiac pacemaker insertion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| cataract operation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| hip arthroplasty | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| inguinal hernia repair | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| spinal operation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| synovial cyst removal | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| tumour excision | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| urethral repair | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| vocal cord operation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| chest pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 4 / 736 (0.54%) | 4 / 735 (0.54%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| non-cardiac chest pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pyrexia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sudden death | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| systemic inflammatory response syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Immune system disorders** | | | |
| drug hypersensitivity | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| seasonal allergy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| **Reproductive system and breast disorders** | | | |
| benign prostatic hyperplasia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed[6] | 1 / 344 (0.29%) | 1 / 354 (0.28%) | 2 / 341 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| postmenopausal haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[7] | 1 / 392 (0.26%) | 0 / 381 (0.00%) | 0 / 397 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| acute respiratory distress syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| asthma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cystic lung disease | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| obstructive airways disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| 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 aspiration | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| pneumothorax | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pulmonary oedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| respiratory arrest | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| sleep apnoea syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| stridor | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| Psychiatric disorders | | | |
| abnormal behaviour | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| acute psychosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 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 | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| agitation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 2 / 735 (0.27%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| anxiety | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| confusional state | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| delirium | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 736 (0.27%) | 5 / 735 (0.68%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| depression | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 4 / 735 (0.54%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| depressive symptom | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 3 / 735 (0.41%) | 0 / 738 (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 |
| device failure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| hallucination | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| hallucination, auditory | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| hallucination, olfactory | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| paranoia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| psychotic disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| schizophrenia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| suicidal ideation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| suicide attempt | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 | | | |
| blood potassium decreased | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| Injury, poisoning and procedural complications | | | |
| accidental overdose | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| accidental poisoning | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| alcohol poisoning | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cervical vertebral fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| chemical burn of gastrointestinal tract | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| clavicle fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| contusion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| fall | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 8 / 736 (1.09%) | 4 / 735 (0.54%) | 6 / 738 (0.81%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| femur fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| femoral neck fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 0 / 738 (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 |
| fibula fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| forearm fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| head injury | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hip fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 3 / 736 (0.41%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 2 / 735 (0.27%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| jaw fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| lacrimal structure injury | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| ligament rupture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| lumbar vertebral fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| multiple injuries | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| overdose | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pelvic fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| periprosthetic fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| post procedural haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| pubis fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| radius fracture<br>alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| rib fracture<br>alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| road traffic accident<br>alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| skin laceration<br>alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| skull fracture<br>alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| spinal compression fracture<br>alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 3 / 738 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| spinal fracture<br>alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| subdural haematoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 3 / 735 (0.41%) | 3 / 738 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| subdural haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| thoracic vertebral fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| tibia fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ulna fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| upper limb fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| wrist fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| gastrointestinal arteriovenous malformation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| Cardiac disorders | | | |
| acute coronary syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 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 / 736 (0.00%) | 2 / 735 (0.27%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| angina pectoris | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| angina unstable | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| atrial fibrillation | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| atrial flutter | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| bifascicular block | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| bradycardia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| cardiac failure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 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 / 736 (0.14%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| cardiac tamponade | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| 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 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| coronary artery thrombosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| myocardial infarction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 0 / 735 (0.00%) | 4 / 738 (0.54%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sinus node dysfunction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sinus bradycardia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| stress cardiomyopathy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| supraventricular extrasystoles | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| supraventricular tachycardia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| tachycardia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| tricuspid valve incompetence | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| **Nervous system disorders** | | | |
| altered state of consciousness | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| central nervous system lesion | | | |
| alternative dictionary used: | | | |

| | | | |
|---|---|---|---|
| MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cerebral haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 2 / 735 (0.27%) | 3 / 738 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| cerebral haematoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| cerebral microhaemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cerebrovascular accident | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 3 / 736 (0.41%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cervical radiculopathy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cholinergic syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| cognitive disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| dementia with lewy bodies | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| dizziness | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| dyskinesia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| epilepsy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| generalised tonic-clonic seizure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| headache | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hypertensive encephalopathy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hypoaesthesia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| intraventricular haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| partial seizures | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| petit mal epilepsy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| presyncope | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sciatica | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| seizure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| subarachnoid haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| syncope | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 6 / 736 (0.82%) | 7 / 735 (0.95%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 3 / 6 | 2 / 7 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| thalamic infarction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| transient ischaemic attack | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 2 / 735 (0.27%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| ulnar nerve palsy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| vasogenic cerebral oedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| vocal cord paresis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| vestibular disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| Eye disorders | | | |
| cataract | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pterygium | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| retinal detachment | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| retinal haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |
| abdominal discomfort | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| alcoholic pancreatitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| anal incontinence | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| coeliac artery stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| colitis microscopic | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| colitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| constipation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| enlarged uvula | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| faecaloma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| femoral hernia incarcerated | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| food poisoning | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| gastric ulcer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| gastritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| gastrooesophageal reflux disease | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| haemorrhoids | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 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 | 2 / 736 (0.27%) | 3 / 735 (0.41%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| intestinal mass | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| intestinal obstruction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 3 / 735 (0.41%) | 0 / 738 (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 |
| large intestine polyp | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lower gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| pancreatitis acute | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| rectal prolapse | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| small intestinal obstruction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| vomiting | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| cholelithiasis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| drug-induced liver injury | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| angioedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| drug eruption | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| psoriasis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| calculus bladder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| urinary retention | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| urge incontinence | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| arthritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 2 / 735 (0.27%) | 0 / 738 (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 |
| back pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| bone lesion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| foot deformity | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| infrapatellar fat pad inflammation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| intervertebral disc compression | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| intervertebral disc protrusion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |

| | | | |
|---|---|---|---|
| lumbar spinal stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| mobility decreased | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| musculoskeletal pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| musculoskeletal chest pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| myofascial pain syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| osteoarthritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 4 / 738 (0.54%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| osteolysis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| osteoporotic fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| pain in extremity | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| spinal column stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| vertebral foraminal stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| **Infections and infestations** | | | |
| appendicitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| bone abscess | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| bronchitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 / 736 (0.14%) | 2 / 735 (0.27%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| clostridium difficile colitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| diverticulitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 3 / 735 (0.41%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| endocarditis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hepatic cyst infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| human anaplasmosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| influenza | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 4 / 735 (0.54%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| intervertebral discitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lower respiratory tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lower respiratory tract infection viral | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| ophthalmic herpes zoster | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| peritonsillitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| pneumonia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 3 / 736 (0.41%) | 3 / 735 (0.41%) | 6 / 738 (0.81%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| sepsis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| septic arthritis streptococcal | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| septic shock | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 3 / 735 (0.41%) | 6 / 738 (0.81%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| urinary tract infection pseudomonal | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| vestibular neuronitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| decreased appetite | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| dehydration | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 4 / 736 (0.54%) | 5 / 735 (0.68%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| electrolyte imbalance | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hypercalcaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 1 / 738 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hyperglycaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 736 (0.00%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 736 (0.27%) | 1 / 735 (0.14%) | 0 / 738 (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 |
| hypokalaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| hypophosphataemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 736 (0.14%) | 0 / 735 (0.00%) | 0 / 738 (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 |
| lactic acidosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 736 (0.00%) | 0 / 735 (0.00%) | 2 / 738 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 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.

[7] - 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 %

| **Non-serious adverse events** | Lanabecestat 20 mg | Lanabecestat 50 mg | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 357 / 736 (48.51%) | 361 / 735 (49.12%) | 340 / 738 (46.07%) |
| Injury, poisoning and procedural complications | | | |
| fall | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 71 / 736 (9.65%) | 73 / 735 (9.93%) | 69 / 738 (9.35%) |
| occurrences (all) | 95 | 111 | 86 |
| Nervous system disorders | | | |
| dizziness | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 43 / 736 (5.84%) | 51 / 735 (6.94%) | 42 / 738 (5.69%) |
| occurrences (all) | 52 | 61 | 48 |
| headache | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 40 / 736 (5.43%) | 46 / 735 (6.26%) | 52 / 738 (7.05%) |
| occurrences (all) | 50 | 72 | 56 |
| Gastrointestinal disorders | | | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 62 / 736 (8.42%) | 54 / 735 (7.35%) | 39 / 738 (5.28%) |
| occurrences (all) | 81 | 62 | 44 |
| nausea | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 33 / 736 (4.48%) | 41 / 735 (5.58%) | 32 / 738 (4.34%) |
| occurrences (all) | 39 | 50 | 38 |
| Respiratory, thoracic and mediastinal disorders | | | |
| cough | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 46 / 736 (6.25%) | 25 / 735 (3.40%) | 25 / 738 (3.39%) |
| occurrences (all) | 49 | 29 | 25 |
| Psychiatric disorders | | | |
| anxiety | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 57 / 736 (7.74%) | 48 / 735 (6.53%) | 34 / 738 (4.61%) |
| occurrences (all) | 63 | 50 | 40 |
| depression | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 36 / 736 (4.89%) | 46 / 735 (6.26%) | 31 / 738 (4.20%) |
| occurrences (all) | 39 | 49 | 32 |
| Musculoskeletal and connective tissue disorders | | | |
| back pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 36 / 736 (4.89%) | 33 / 735 (4.49%) | 40 / 738 (5.42%) |
| occurrences (all) | 38 | 35 | 50 |
| Infections and infestations | | | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 78 / 736 (10.60%) | 76 / 735 (10.34%) | 60 / 738 (8.13%) |
| occurrences (all) | 94 | 89 | 69 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 39 / 736 (5.30%) | 44 / 735 (5.99%) | 46 / 738 (6.23%) |
| occurrences (all) | 43 | 50 | 57 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 36 / 736 (4.89%)<br>53 | 32 / 735 (4.35%)<br>36 | 56 / 738 (7.59%)<br>70 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 March 2015 | Amendment (04): Protocol amended to specify<br>-Co-administration of AZD3293 with food is now permitted.<br>-Wording for permitted dose changes for cholinesterase inhibitors has been modified from "reductions" to "adjustments" to allow increases in dose if medically necessary.<br>-Antipsychotic are no longer prohibited to allow treatment of patients if medically necessary. |
| 30 June 2016 | Amendment (07):<br>- Changed the primary endpoint CDR-SB to ADAS-Cog13.<br>-Updated potential risks to be consistent with the Investigator's Brochure (IB): Initiation of symptomatic treatments for patient progression (including acetylcholinesterase inhibitors [AChEI] and memantine) to now to be permitted at specific time intervals.<br>-Broadened classes of applicable medications and added clinical judgment to Exclusion Criterion [26] about use of concomitant medications during study participation. |
| 12 July 2017 | Amendment (7.1): Added a fourth interim analysis with description. Clarified timing of third and fourth interim analysis. |

Notes:

## 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. Due to early termination of the study the planned population PK analysis was not performed.

Notes: