# Clinical trial results:
# A Phase 3 Clinical Study to Investigate the Prevention of Relapse in Lymphoma Using Daily Enzastaurin

## Summary

| | |
|---|---|
| EudraCT number | 2005-004630-41 |
| Trial protocol | SE HU ES DK BE PT DE GR IT GB CZ FI |
| Global end of trial date | 31 July 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 June 2018 |
| First version publication date | 15 June 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | H6Q-MC-JCBJ |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00332202 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number : 9823 |

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, 1 877-CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559, |

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 | 31 July 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 31 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Main objective: To compare maintenance therapy with enzastaurin versus placebo, in terms of the overall disease-free survival (DFS) time in patients with DLBCL in first remission with high risk of relapse (initial IPI score ≥3) following R-CHOP using a 14- or 21-day

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 May 2006 |
| 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 | Portugal: 8 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Sweden: 24 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | Denmark: 13 |
| Country: Number of subjects enrolled | Finland: 16 |
| Country: Number of subjects enrolled | France: 32 |
| Country: Number of subjects enrolled | Germany: 25 |
| Country: Number of subjects enrolled | Greece: 4 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Australia: 29 |
| Country: Number of subjects enrolled | Brazil: 18 |
| Country: Number of subjects enrolled | Canada: 40 |
| Country: Number of subjects enrolled | China: 25 |
| Country: Number of subjects enrolled | India: 33 |
| Country: Number of subjects enrolled | Korea, Republic of: 58 |

| | |
|---|---|
| Country: Number of subjects enrolled | Mexico: 22 |
| Country: Number of subjects enrolled | Puerto Rico: 4 |
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Taiwan: 32 |
| Country: Number of subjects enrolled | United States: 186 |
| Country: Number of subjects enrolled | Japan: 87 |
| Worldwide total number of subjects | 758 |
| EEA total number of subjects | 224 |

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) | 404 |
| From 65 to 84 years | 348 |
| 85 years and over | 6 |

## Subject disposition

### Recruitment

Recruitment details:

No text entered

### Pre-assignment

Screening details:

No text entered

### 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, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Enzastaurin: Arm A - Experimental |

Arm description:

Enzastaurin 500 milligram (mg) administered orally (PO) each day (QD) after an initial loading dose of 1125 mg on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Enzastaurin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1125 mg enzastaurin loading dose given oral (PO on Day 1), then 500 mg enzastaurin given PO daily (QD) until disease progression or maximum of 3 years.

| | |
|---|---|
| **Arm title** | Placebo: Arm B - Control |

Arm description:

Placebo administered PO QD after an initial loading dose of placebo on Day 1.

| | |
|---|---|
| Arm type | Control |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo administered PO QD after an initial loading dose of placebo on Day 1.

| **Number of subjects in period 1** | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control |
|---|---|---|
| Started | 504 | 254 |
| Received At Least One Dose of Study Drug | 493 | 249 |
| Completed | 263 | 129 |
| Not completed | 241 | 125 |
| Physician decision | 6 | 8 |
| Protocol entry criteria not met | 6 | 5 |
| Consent withdrawn by subject | 36 | 17 |
| Adverse event, non-fatal | 72 | 28 |
| Protocol violation | 7 | 2 |
| Death | 5 | 2 |
| Lost to follow-up | 2 | 1 |
| Sponsor decision | 1 | 2 |
| Progressive disease | 106 | 60 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Enzastaurin: Arm A - Experimental |
| Reporting group description: | |
| Enzastaurin 500 milligram (mg) administered orally (PO) each day (QD) after an initial loading dose of 1125 mg on Day 1. | |
| Reporting group title | Placebo: Arm B - Control |
| Reporting group description: | |
| Placebo administered PO QD after an initial loading dose of placebo on Day 1. | |

| Reporting group values | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | Total |
|---|---|---|---|
| Number of subjects | 504 | 254 | 758 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.19 | 62.65 | |
| standard deviation | ± 13.13 | ± 12.09 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 245 | 105 | 350 |
| Male | 259 | 149 | 408 |
| Region of Enrollment<br>Units: Subjects | | | |
| Australia | 20 | 9 | 29 |
| Belgium | 10 | 4 | 14 |
| Brazil | 13 | 5 | 18 |
| Canada | 24 | 16 | 40 |
| China | 18 | 7 | 25 |
| Czech Republic | 6 | 2 | 8 |
| Germany | 15 | 10 | 25 |
| Denmark | 9 | 4 | 13 |
| Spain | 20 | 5 | 25 |
| Finland | 11 | 5 | 16 |
| France | 22 | 10 | 32 |
| Greece | 2 | 2 | 4 |
| Hungary | 4 | 2 | 6 |
| India | 22 | 11 | 33 |
| Italy | 15 | 10 | 25 |
| Japan | 54 | 33 | 87 |
| Korea, Republic of | 37 | 21 | 58 |
| Mexico | 13 | 9 | 22 |
| Poland | 9 | 7 | 16 |
| Puerto Rico | 3 | 1 | 4 |
| Portugal | 5 | 3 | 8 |
| Sweden | 19 | 5 | 24 |
| Taiwan | 24 | 8 | 32 |

| | | | |
|---|---|---|---|
| United Kingdom | 4 | 4 | 8 |
| United States | 125 | 61 | 186 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| African | 5 | 2 | 7 |
| Caucasian | 309 | 155 | 464 |
| East Asian | 144 | 73 | 217 |
| Hispanic | 24 | 13 | 37 |
| Native American | 1 | 0 | 1 |
| West Asian (Indian sub-continent) | 21 | 11 | 32 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Enzastaurin: Arm A - Experimental |

Reporting group description:

Enzastaurin 500 milligram (mg) administered orally (PO) each day (QD) after an initial loading dose of 1125 mg on Day 1.

| | |
|---|---|
| Reporting group title | Placebo: Arm B - Control |

Reporting group description:

Placebo administered PO QD after an initial loading dose of placebo on Day 1.

| | |
|---|---|
| Subject analysis set title | Germinal-center B-cells |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Reported are the DFS based on DLBCL molecular subtypes. DLBCL molecular subtypes of GCB/non-GCB using Hans' algorithm were determined by protein expression by immunohistochemistry (IHC) of cluster differentiation 10 (CD10), B-cell/lymphoma 6 (BCL6) and multiple myeloma oncogene 1 (MUM1) for percent of tumor cells stained, and using 30% positive staining as the cutoff for positive/negative.

Analysis Population Description: All randomized participants for which a pre-treatment tumor tissue was provided and had evaluable samples.

| | |
|---|---|
| Subject analysis set title | Non-germinal-center B-cells |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Reported are the DFS based on DLBCL molecular subtypes. DLBCL molecular subtypes of GCB/non-GCB using Hans' algorithm were determined by protein expression by immunohistochemistry (IHC) of cluster differentiation 10 (CD10), B-cell/lymphoma 6 (BCL6) and multiple myeloma oncogene 1 (MUM1) for percent of tumor cells stained, and using 30% positive staining as the cutoff for positive/negative.

Analysis Population Description: All randomized participants for which a pre-treatment tumor tissue was provided and had evaluable samples.

| | |
|---|---|
| Subject analysis set title | PKC-β2 Cytoplasm |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Reported are the DFS based on PKC-β2 protein expression. Immunohistochemistry (IHC) staining was performed to assess protein expression of PKC-β2 in cytoplasm scored for percent of tumor cells stained, and using 50% positive staining as the cutoff for high/low expression (high expression: >=50% staining, low expression: <50% staining).

Analysis Population Definition: All randomized participants for which a pre-treatment tumor tissue was provided and had evaluable samples.

| | |
|---|---|
| Subject analysis set title | Total Enzastaurin Population |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Analysis Population Description: All participants who received at least one dose of the study drug and had evaluable PK data.

### Primary: Overall Disease-Free Survival

| | |
|---|---|
| End point title | Overall Disease-Free Survival |

End point description:

Overall Disease-Free Survival (DFS) time is defined as the time from the date of study enrollment to the first date of objectively determined disease recurrence (progressive disease) or death from any cause. DFS was assessed according to International Working Group recommendations (Cheson et al. 1999). Progressive disease (PD) is defined as a ≥ 50% increase from the lowest point in the sum of the product of the diameters (SPD) of any previously identified abnormal node for partial or nonresponders, or the appearance of any new lesion during or at the end of therapy.

Analysis Population Description: All randomized participants. DFS is censored at the last assessable disease free assessment for participants who are alive or have not progressed. The number of censored participant data for enzastaurin and placebo is 369 (73.2%) and 180 (70.9%), respectively.

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

End point timeframe:

Baseline to Measured Progressive Disease or Death from Any Cause (up to 80.30 months)

| **End point values** | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 504[1] | 254[2] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[1] - Median, the upper & lower 95% confidence interval were not estimable due to high rate of censoring.
[2] - Median, the upper & lower 95% confidence interval were not estimable due to high rate of censoring.

### Statistical analyses

| **Statistical analysis title** | Overall Disease-Free Survival |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 758 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.541 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.689 |
| upper limit | 1.216 |

## Secondary: Disease Free Survival at 2 Years

| End point title | Disease Free Survival at 2 Years |
|---|---|

End point description:

Disease-free survival at 2 years (DFS2) is defined as the rate of DFS at 2 years from the date of study enrollment and is determined using the distribution of overall DFS times. Disease-free survival rates at 2 years will be estimated using the Kaplan-Meier method.

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

End point timeframe:

Baseline to 2 Years

| End point values | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 504[3] | 254[4] | | |
| Units: Rate | | | | |
| number (confidence interval 95%) | 0.785 (0.745 to 0.819) | 0.748 (0.687 to 0.798) | | |

Notes:

[3] - All randomized participants.

[4] - All randomized participants.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Event-Free Survival

| End point title | Event-Free Survival |
|---|---|

End point description:

Overall Event-Free Survival (EFS) time is defined as the time from the date of study enrollment to the first date of objectively determined disease recurrence (progressive disease), institution of a new anti-cancer treatment, or death from any cause. Progressive disease (PD) is defined as a ≥ 50% increase from the lowest point in the sum of the product of the diameters (SPD) of any previously identified abnormal node for partial or nonresponders, or the appearance of any new lesion during or at the end of therapy.

Analysis Population Description: All randomized participants. EFS is censored at the last assessable disease-free assessment for participants who are alive, have not progressed or started new anticancer treatment. The number of censored participant data for enzastaurin and placebo is 364 (72.2%) and 176 (69.3%), respectively.

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

End point timeframe:

Baseline to Objective PD, Start of New Therapy or Death From Any Cause (up to 76.81 months)

| End point values | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 504[5] | 254[6] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[5] - Median, the upper & lower 95% confidence interval were not estimable due to high rate of censoring.

[6] - Median, the upper & lower 95% confidence interval were not estimable due to high rate of censoring.

### Statistical analyses

| Statistical analysis title | Event-Free Survival |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |

| | |
|---|---|
| Number of subjects included in analysis | 758 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.683 |
| upper limit | 1.188 |

## Secondary: Event-Free Survival at 2 Years

| | |
|---|---|
| End point title | Event-Free Survival at 2 Years |

End point description:

Event-Free Survival at 2 years (EFS2) is defined as the rate of EFS at 2 years from the date of study enrollment and is determined using the distribution of overall EFS times. Event-free survival rates at 2 years will be estimated using the Kaplan-Meier method.

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

End point timeframe:

Baseline to 2 Years

| End point values | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 504[7] | 254[8] | | |
| Units: Rate | | | | |
| number (confidence interval 95%) | 0.781 (0.741 to 0.816) | 0.734 (0.673 to 0.785) | | |

Notes:

[7] - All randomized participants.

[8] - All randomized participants.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

| | |
|---|---|
| End point title | Overall Survival |

End point description:

Overall survival (OS) time is defined as the time from the date of study enrollment to the date of death from any cause.

Analysis Population Description: All randomized participants. Overall survival is censored at the last date of contact for participants who have no reported death. The number of censored participant data for enzastaurin and placebo is 404 (80.2%) and 205 (80.7%), respectively.

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

End point timeframe:

Baseline to Date of Death from Any Cause (up to 80.30 months)

| **End point values** | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 504[9] | 254[10] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[9] - Median, the upper & lower 95% confidence interval were not estimable due to high rate of censoring.
[10] - Median, the upper & lower 95% confidence interval were not estimable due to high rate of censoring.

### Statistical analyses

| **Statistical analysis title** | Overall Survival |
|---|---|
| Comparison groups | Placebo: Arm B - Control v Enzastaurin: Arm A - Experimental |
| Number of subjects included in analysis | 758 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.807 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.741 |
| upper limit | 1.468 |

## Secondary: Number of Participants With Treatment-Emergent Adverse Events

| End point title | Number of Participants With Treatment-Emergent Adverse Events |
|---|---|

End point description:

Number of treatment-emergent adverse events occurring in at least 10% of participants regardless of causality.

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

End point timeframe:

First dose through 30 days post-study treatment discontinuation (up to 81.30 months)

| End point values | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 493[11] | 249[12] | | |
| Units: Participants | | | | |
| number (not applicable) | 459 | 230 | | |

Notes:

[11] - All randomized participants who received at least one dose of study drug.

[12] - All randomized participants who received at least one dose of study drug.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Quality of Life: Change From Baseline in Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) Score

| End point title | Quality of Life: Change From Baseline in Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) Score |
|---|---|

End point description:

The FACT-Lym (Cella et al. 2005) assesses health-related quality of life (HRQoL) in participants with non-Hodgkin lymphoma. It includes the 27-item cancer-specific FACT-G (General), which assesses physical, social/family, emotional and functional well-being, plus a 15-item subscale that assesses concerns specific to lymphoma. Each item is scored on a scale from 0 (not at all) to 4 (very much), yielding a possible score of 0-168, with higher scores representing better HRQoL. This analysis utilized mixed-effect model repeated measure (MMRM) analysis of change from baseline adjusting for baseline covariates.

Analysis Population Description: All randomized participants who completed at least one FACT-Lym assessment.

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

End point timeframe:

Baseline, Month 2; Baseline, Month 4; Baseline, Month 6; Baseline, Month 12; Baseline, Month 18; Baseline, Month 24; Baseline, Month 36

| End point values | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 348 | 189 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 2 | 2.45 (± 0.67) | 1.86 (± 0.93) | | |
| Month 4 | 2.56 (± 0.8) | 2.51 (± 1.06) | | |
| Month 6 | 2.04 (± 0.87) | 2.82 (± 1.1) | | |
| Month 12 | 3.85 (± 0.87) | 2.11 (± 1.29) | | |
| Month 18 | 2.87 (± 0.89) | 1.73 (± 1.26) | | |
| Month 24 | 2.72 (± 0.99) | 3.96 (± 1.26) | | |
| Month 36 | 2.54 (± 1.13) | 4.22 (± 1.43) | | |

**Statistical analyses**

| **Statistical analysis title** | FACT-Lym Score Month 2 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.606 |
| Method | Mixed models analysis |

| **Statistical analysis title** | FACT-Lym Score Month 4 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.971 |
| Method | Mixed models analysis |

| **Statistical analysis title** | Fact-Lym Score Month 6 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | Mixed models analysis |

| **Statistical analysis title** | FACT-Lym Score Month 12 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.265 |
| Method | Mixed models analysis |

| **Statistical analysis title** | FACT-Lym Score Month 18 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |

| | |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 |
| Method | Mixed models analysis |

| **Statistical analysis title** | FACT-Lym Score Month 24 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.441 |
| Method | Mixed models analysis |

| **Statistical analysis title** | FACT-Lym Score Month 36 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.357 |
| Method | Mixed models analysis |

**Secondary: Change From Baseline in EuroQol-5D (EQ-5D) Score**

| End point title | Change From Baseline in EuroQol-5D (EQ-5D) Score |
|---|---|

End point description:

The EQ-5D instrument is a participant-rated questionnaire used to evaluate health status. The EQ-5D assesses five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) that participants rate using three levels (no problem, some problem, or extreme problem), as well as overall health status. The five dimensions can be combined using country-specific weights to create an estimate of overall health status. This analysis utilized mixed-effect model repeated measure (MMRM) analysis of change from baseline in the EQ-5D for the United Kingdom population-based index score adjusting for baseline covariates.

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

End point timeframe:

Baseline, Month 6; Baseline, Month 24; Baseline, Month 33

| **End point values** | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346[13] | 187[14] | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| Month 6 | 0.02 (± 0.01) | 0 (± 0.01) | | |
| Month 24 | 0.02 (± 0.01) | 0.03 (± 0.02) | | |
| Month 33 | 0.03 (± 0.01) | 0.03 (± 0.01) | | |

Notes:

[13] - All randomized participants who completed at least one EQ-5D assessment.

[14] - All randomized participants who completed at least one EQ-5D assessment.

### Statistical analyses

| **Statistical analysis title** | EuroQol-5D Score Month 6 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 533 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.267 |
| Method | Mixed models analysis |

| **Statistical analysis title** | EuroQol-5D Score Month 24 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 533 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.807 |
| Method | Mixed models analysis |

| **Statistical analysis title** | EuroQol-5D Score Month 33 |
|---|---|
| Comparison groups | Enzastaurin: Arm A - Experimental v Placebo: Arm B - Control |
| Number of subjects included in analysis | 533 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.864 |
| Method | Mixed models analysis |

## Secondary: Translational Research: DFS of Participants With Diffuse Large B-cell Lymphoma (DLBCL) Germinal-center B-cells (GCB) Versus Non-GCB Molecular Subtypes

| End point title | Translational Research: DFS of Participants With Diffuse Large B-cell Lymphoma (DLBCL) Germinal-center B-cells (GCB) Versus Non-GCB Molecular Subtypes |
|---|---|

End point description:

Reported are the DFS based on DLBCL molecular subtypes. DLBCL molecular subtypes of GCB/non-GCB using Hans' algorithm were determined by protein expression by immunohistochemistry (IHC) of cluster differentiation 10 (CD10), B-cell/lymphoma 6 (BCL6) and multiple myeloma oncogene 1 (MUM1) for percent of tumor cells stained, and using 30% positive staining as the cutoff for positive/negative.

Analysis Population Description: All randomized participants for which a pre-treatment tumor tissue was provided and had evaluable samples.

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: Baseline | |

| End point values | Germinal-center B-cells | Non-germinal-center B-cells | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 | 106 | | |
| Units: Participants | | | | |
| number (not applicable) | 109 | 106 | | |

### Statistical analyses

| Statistical analysis title | Germinal-center versus Non-germinal-center B-cells |
|---|---|
| Comparison groups | Germinal-center B-cells v Non-germinal-center B-cells |
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.74 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.52 |

Notes:

[15] - Cox regression of DFS (for the combined treatment arm) for DLBCL molecular subtypes as a function of molecular subtype, treatment, adjusting for covariates of International Prognostic Index (IPI) score (<=3 vs. >3), age (<=60 vs. > 60) and Prior Radiation (yes vs. no).

### Secondary: Translational Research: DFS of Participants With Diffuse Large B-cell Lymphoma (DLBCL) Protein Kinase C-β2 (PKC-β2) Expression

| End point title | Translational Research: DFS of Participants With Diffuse Large B-cell Lymphoma (DLBCL) Protein Kinase C-β2 (PKC-β2) Expression |
|---|---|

End point description:

Reported are the DFS based on PKC-β2 protein expression. Immunohistochemistry (IHC) staining was performed to assess protein expression of PKC-β2 in cytoplasm scored for percent of tumor cells stained, and using 50% positive staining as the cutoff for high/low expression (high expression: >=50% staining, low expression: <50% staining).

Analysis Population Description: All randomized participants for which a pre-treatment tumor tissue was provided and had evaluable samples.

Statistical Analysis: The PKC-β2 Cytoplasm expression summary statistics is reported as the combined Enzastaurin and Placebo reporting groups for which an evaluable pre-treatment tumor tissue sample was provided. Although the statistical analysis has been performed, it is not reported here as at least two comparison groups are required.

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

End point timeframe:

Baseline

| End point values | PKC-β2 Cytoplasm | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 227[16] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| High Cytoplasmic Expression | 60 | | | |
| Low Cytoplasmic Expression | 167 | | | |

Notes:

[16] - PKC-B2 stats analysis performed on combined tx arms, however requires 2 comparison groups to report.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics: Average Steady-State Concentration (Cavg,ss) for Total Analyte

| End point title | Pharmacokinetics: Average Steady-State Concentration (Cavg,ss) for Total Analyte |
|---|---|

End point description:

Analysis Population Description: All participants who received at least one dose of the study drug and had evaluable PK data.

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

End point timeframe:

Month 2, Month 4

| End point values | Total Enzastaurin Population | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 328 | | | |
| Units: Nanomole/liter (nmol/L) | | | | |
| geometric mean (geometric coefficient of variation) | 2370 (± 59.9) | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Entire Study | |
| Adverse event reporting additional description: | |
| H6Q-MC-JCBJ | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Enzastaurin: Arm A - Experimental |
| Reporting group description: | |
| Enzastaurin 500 mg administered orally PO QD after an initial loading dose of 1125 mg on Day 1. | |
| Reporting group title | Placebo: Arm B - Control |
| Reporting group description: | |
| Placebo administered PO QD after an initial loading dose of placebo on Day 1. | |

| Serious adverse events | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 135 / 493 (27.38%) | 72 / 249 (28.92%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| acute myeloid leukaemia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| basal cell carcinoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast cancer in situ | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebellar tumour | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colon adenoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colon cancer | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 9 / 9 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diffuse large b-cell lymphoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastric cancer | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| hepatic cancer metastatic | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 9 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| hypopharyngeal cancer | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| large intestine carcinoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lung neoplasm | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lung neoplasm malignant | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| multiple myeloma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myelodysplastic syndrome | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ovarian neoplasm | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[1] | 1 / 239 (0.42%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pancreatic neoplasm | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| prostate cancer | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed[2] | 1 / 254 (0.39%) | 0 / 146 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| rectal cancer | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| salivary gland adenoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| squamous cell carcinoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 18 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thyroid neoplasm | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Vascular disorders | | | |
| aortic aneurysm | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deep vein thrombosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 4 / 493 (0.81%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 21 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypotension | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| abdominal hernia repair | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| anal fissure excision | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| meniscus removal | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| spinal fusion surgery | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| chest pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| death | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| general physical health deterioration | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| multi-organ failure | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| multi-organ disorder | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| spinal pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| allergy to arthropod sting | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| contrast media allergy | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| prostatic obstruction | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[3] | 1 / 254 (0.39%) | 0 / 146 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| prostatitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed[4] | 1 / 254 (0.39%) | 0 / 146 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| acute pulmonary oedema | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| asthma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| interstitial lung disease | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lung infiltration | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pleural effusion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pleurisy | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 8 / 493 (1.62%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 4 / 23 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| delirium | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| depression | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| aspartate aminotransferase increased | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ejection fraction decreased | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| electrocardiogram abnormal | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| electrocardiogram qt prolonged | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 12 / 12 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| acetabulum fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cervical vertebral fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| concussion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fall | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hip fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lumbar vertebral fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| maternal exposure during pregnancy | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed[5] | 2 / 239 (0.84%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| radius fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| road traffic accident | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| spinal compression fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subdural haematoma | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tendon rupture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tibia fracture | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| acute coronary syndrome | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| angina pectoris | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| angina unstable | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| arrhythmia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| atrial fibrillation | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| atrial flutter | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| atrioventricular block complete | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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|---|---|---|---|---|
| bradycardia | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| cardiac arrest | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| cardiac failure | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 2 / 249 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 16 | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| cardiac failure chronic | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| cardiac failure congestive | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 2 / 249 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| cardio-respiratory arrest | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| cardiomyopathy | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 493 (0.61%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 25 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| coronary artery disease | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| coronary artery stenosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| left ventricular dysfunction | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 6 / 6 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myocardial ischaemia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myocardial infarction | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| sick sinus syndrome | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| sinus bradycardia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| torsade de pointes | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ventricular fibrillation | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ventricular tachycardia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| **Nervous system disorders** | | | |
| basal ganglia infarction | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebral haemorrhage | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| convulsion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cranial nerve paralysis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dysaesthesia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| epilepsy | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| grand mal convulsion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| headache | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoaesthesia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| hypoxic-ischaemic encephalopathy | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ischaemic stroke | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| nerve root compression | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neuropathy peripheral | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| posterior reversible encephalopathy syndrome | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sciatica | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| syncope | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 6 / 493 (1.22%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tongue paralysis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tonic convulsion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| transient ischaemic attack | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vith nerve paralysis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vocal cord paralysis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 5 / 493 (1.01%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| febrile neutropenia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 6 / 493 (1.22%) | 3 / 249 (1.20%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| leukopenia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lymphadenopathy | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutropenia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| vertigo | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| cataract | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 493 (0.41%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| conjunctival haemorrhage | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| eyelid ptosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ophthalmoplegia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| retinal detachment | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| retinal vein occlusion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vision blurred | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Gastrointestinal disorders | | | |
| abdominal pain upper | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| anal prolapse | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colonic polyp | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| constipation | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dysphagia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 493 (0.00%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| food poisoning | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastritis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal obstruction | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gingivitis ulcerative | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhoids | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ileus | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | | |
|---|---|---|---|---|
| ileus paralytic | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| inguinal hernia | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| intestinal obstruction | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| jejunal perforation | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| nausea | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| oral lichen planus | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 11 / 11 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| pancreatitis | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pancreatitis acute | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pseudopolyposis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| small intestinal obstruction | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subileus | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| umbilical hernia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| volvulus of small bowel | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| vomiting | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| cholecystitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholecystitis acute | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholelithiasis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 4 / 493 (0.81%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic cirrhosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic function abnormal | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| hepatotoxicity | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| dermal cyst | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| skin fibrosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| skin ulcer | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| calculus ureteric | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hydronephrosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| incontinence | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oliguria | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal failure | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal failure acute | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urinary retention | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| arthralgia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| back pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemarthrosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intervertebral disc protrusion | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myalgia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neck pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteoarthritis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 21 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| osteolysis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pain in extremity | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| plantar fasciitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| abdominal sepsis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| arthritis infective | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| beta haemolytic streptococcal infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bronchitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bronchopulmonary aspergillosis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bronchopneumonia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cellulitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cervicitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed[6] | 1 / 239 (0.42%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| clostridium difficile colitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| enterocolitis infectious | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| enteritis infectious | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| escherichia sepsis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| escherichia urinary tract infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| helicobacter gastritis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 2 / 249 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic cyst infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatitis b | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 493 (0.00%) | 3 / 249 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| hepatitis c | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| herpes zoster | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infectious peritonitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intervertebral discitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lobar pneumonia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| lung infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myelitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| necrotising fasciitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| neutropenic infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| periodontitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 6 / 493 (1.22%) | 7 / 249 (2.81%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| pseudomembranous colitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pseudomonal bacteraemia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pyelonephritis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| respiratory tract infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| scrub typhus | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sepsis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 5 / 493 (1.01%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| septic shock | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | | |
|---|---|---|---|---|
| staphylococcal infection | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| urinary tract infection | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 3 / 493 (0.61%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| urosepsis | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| viral upper respiratory tract infection | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 1 / 493 (0.20%) | 0 / 249 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| wound infection | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Metabolism and nutrition disorders | | | | |
| decreased appetite | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |
| subjects affected / exposed | 0 / 493 (0.00%) | 1 / 249 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| dehydration | | | | |
| alternative dictionary used: MedDRA 15.1 | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 493 (0.20%) | 1 / 249 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 2 / 493 (0.41%) | 0 / 249 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

| **Non-serious adverse events** | Enzastaurin: Arm A - Experimental | Placebo: Arm B - Control | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 447 / 493 (90.67%) | 221 / 249 (88.76%) | |
| Vascular disorders | | | |
| hypertension | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 8 / 493 (1.62%) | 13 / 249 (5.22%) | |
| occurrences (all) | 64 | 127 | |
| General disorders and administration site conditions | | | |
| fatigue | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 91 / 493 (18.46%) | 45 / 249 (18.07%) | |
| occurrences (all) | 628 | 304 | |
| oedema peripheral | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 63 / 493 (12.78%) | 16 / 249 (6.43%) | |
| occurrences (all) | 370 | 84 | |
| pyrexia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 34 / 493 (6.90%) | 16 / 249 (6.43%) | |
| occurrences (all) | 60 | 21 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| cough | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 76 / 493 (15.42%) | 30 / 249 (12.05%) | |
| occurrences (all) | 283 | 130 | |
| oropharyngeal pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 26 / 493 (5.27%) | 7 / 249 (2.81%) | |
| occurrences (all) | 84 | 14 | |
| Psychiatric disorders | | | |
| insomnia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 40 / 493 (8.11%) | 13 / 249 (5.22%) | |
| occurrences (all) | 327 | 107 | |
| Investigations | | | |
| alanine aminotransferase increased | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 27 / 493 (5.48%) | 12 / 249 (4.82%) | |
| occurrences (all) | 148 | 73 | |
| aspartate aminotransferase increased | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 29 / 493 (5.88%) | 12 / 249 (4.82%) | |
| occurrences (all) | 191 | 52 | |
| electrocardiogram qt prolonged | | | |
| alternative dictionary used: | | | |

| | | | |
|---|---|---|---|
| MedDRA 15.1 | | | |
| subjects affected / exposed | 54 / 493 (10.95%) | 11 / 249 (4.42%) | |
| occurrences (all) | 317 | 44 | |
| weight increased | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 24 / 493 (4.87%) | 19 / 249 (7.63%) | |
| occurrences (all) | 194 | 149 | |
| Nervous system disorders | | | |
| dizziness | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 53 / 493 (10.75%) | 21 / 249 (8.43%) | |
| occurrences (all) | 238 | 129 | |
| headache | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 49 / 493 (9.94%) | 32 / 249 (12.85%) | |
| occurrences (all) | 295 | 189 | |
| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 33 / 493 (6.69%) | 13 / 249 (5.22%) | |
| occurrences (all) | 221 | 79 | |
| leukopenia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 27 / 493 (5.48%) | 11 / 249 (4.42%) | |
| occurrences (all) | 87 | 45 | |
| neutropenia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 52 / 493 (10.55%) | 26 / 249 (10.44%) | |
| occurrences (all) | 143 | 66 | |
| Gastrointestinal disorders | | | |
| abdominal pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 40 / 493 (8.11%) | 12 / 249 (4.82%) | |
| occurrences (all) | 140 | 20 | |
| constipation | | | |
| alternative dictionary used: | | | |

| | | | |
|---|---|---|---|
| MedDRA 15.1 | | | |
| subjects affected / exposed | 49 / 493 (9.94%) | 20 / 249 (8.03%) | |
| occurrences (all) | 256 | 101 | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 97 / 493 (19.68%) | 33 / 249 (13.25%) | |
| occurrences (all) | 387 | 115 | |
| dry mouth | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 25 / 493 (5.07%) | 5 / 249 (2.01%) | |
| occurrences (all) | 177 | 44 | |
| faeces discoloured | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 39 / 493 (7.91%) | 0 / 249 (0.00%) | |
| occurrences (all) | 340 | 0 | |
| nausea | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 73 / 493 (14.81%) | 38 / 249 (15.26%) | |
| occurrences (all) | 195 | 150 | |
| vomiting | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 47 / 493 (9.53%) | 26 / 249 (10.44%) | |
| occurrences (all) | 64 | 44 | |
| Skin and subcutaneous tissue disorders | | | |
| pruritus | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 51 / 493 (10.34%) | 21 / 249 (8.43%) | |
| occurrences (all) | 329 | 104 | |
| rash | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 56 / 493 (11.36%) | 27 / 249 (10.84%) | |
| occurrences (all) | 323 | 120 | |
| Renal and urinary disorders | | | |
| chromaturia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 96 / 493 (19.47%) | 1 / 249 (0.40%) | |
| occurrences (all) | 916 | 13 | |
| Musculoskeletal and connective tissue disorders | | | |
| arthralgia | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 43 / 493 (8.72%) | 28 / 249 (11.24%) | |
| occurrences (all) | 368 | 238 | |
| back pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 52 / 493 (10.55%) | 24 / 249 (9.64%) | |
| occurrences (all) | 353 | 213 | |
| musculoskeletal pain | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 32 / 493 (6.49%) | 15 / 249 (6.02%) | |
| occurrences (all) | 263 | 107 | |
| pain in extremity | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 36 / 493 (7.30%) | 17 / 249 (6.83%) | |
| occurrences (all) | 173 | 71 | |
| Infections and infestations | | | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 37 / 493 (7.51%) | 13 / 249 (5.22%) | |
| occurrences (all) | 112 | 34 | |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 42 / 493 (8.52%) | 15 / 249 (6.02%) | |
| occurrences (all) | 80 | 47 | |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 27 / 493 (5.48%) | 7 / 249 (2.81%) | |
| occurrences (all) | 93 | 13 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| decreased appetite | | | |
| alternative dictionary used: MedDRA 15.1 | | | |
| subjects affected / exposed | 34 / 493 (6.90%) | 14 / 249 (5.62%) | |
| occurrences (all) | 151 | 56 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 October 2009 | Amendment E: Protocol has been amended to modify ECG monitoring in response to the US FDA's recommendation, based on enzastaurin-associated QTc prolongation. |
| 24 September 2012 | Amendment G: Revised database lock, based on agreement from the United States Food and Drug Administration (FDA), to change the primary endpoint from a pre-specified number of events (event-driven) to a fixed cut-off date (time-driven). Due to a slower than originally expected pooled event rate in this study, the protocol has been revised so that the primary analysis of the DFS endpoint will occur at LPET+3 years. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported