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 Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.19	62.65	
standard deviation	± 13.13	± 12.09	-
Gender categorical Units: Subjects			
Female	245	105	350
Male	259	149	408
Region of Enrollment 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 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	

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				

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	

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	

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			

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			

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			

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	

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			

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	

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			

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			

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			

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			

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	

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