Clinical trial results:
A Randomized Phase 3 Study of Enzastaurin versus Lomustine in the Treatment of Recurrent, Intracranial Glioblastoma Multiforme

Summary

EudraCT number	2005-004627-18
Trial protocol	AT ES DE BE GB IT
Global end of trial date	23 May 2014

Results information

Result version number	v1 (current)
This version publication date	29 November 2018
First version publication date	29 November 2018

Trial information

Trial identification

Sponsor protocol code	H6Q-MC-JCBF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00295815
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 9817

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, 877 CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 877 285 4559,
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, 877 CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 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	23 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare enzastaurin versus lomustine in terms of PFS time in patients with recurrent, intracranial GBM (WHO Stage IV).

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	10 January 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Ethical reason
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	United States: 77

Worldwide total number of subjects	266
EEA total number of subjects	131

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)	221
From 65 to 84 years	45
85 years and over	0

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	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	500 mg Enzastaurin

Arm description:

500 mg enzastaurin administered daily oral dose (four 125-mg tablets once a day) starting on Day 2 with an 1125-mg loading dose (three 125-mg tablets taken 3 times a day).

Arm type	Experimental
Investigational medicinal product name	Enzastaurin
Investigational medicinal product code	
Other name	LY317615
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg enzastaurin administered daily (four 125-mg tablets once a day) starting on Day 2 with an 1125-mg loading dose (three 125-mg tablets taken 3 times a day).

Arm title	Lomustine

Arm description:

10 mg, 40 mg, or 100 mg lomustine administered orally as 100 to 130 mg/m2 on Day 1 of each 6-week treatment cycle.

Arm type	Active comparator
Investigational medicinal product name	Lomustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg, 40 mg, or 100 mg lomustine administered orally as 100 to 130 mg/m2 on Day 1 of each 6-week treatment cycle.

Number of subjects in period 1	500 mg Enzastaurin	Lomustine
Started	174	92
Received at least one dose of study drug	167	84
Completed	157	74
Not completed	17	18
Consent withdrawn by subject	5	4
Physician decision	-	2
Not Treated	7	10
Sponsor Decision	4	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	500 mg Enzastaurin
Reporting group description:	
500 mg enzastaurin administered daily oral dose (four 125-mg tablets once a day) starting on Day 2 with an 1125-mg loading dose (three 125-mg tablets taken 3 times a day).	
Reporting group title	Lomustine
Reporting group description:	
10 mg, 40 mg, or 100 mg lomustine administered orally as 100 to 130 mg/m2 on Day 1 of each 6-week treatment cycle.	

Reporting group values	500 mg Enzastaurin	Lomustine	Total
Number of subjects	174	92	266
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
All participants who received at least one dose of study drug.			
Units: years			
arithmetic mean	55.6	54.0	
standard deviation	± 10.98	± 12.52	-
Gender categorical Units: Subjects			
Female	58	36	94
Male	116	56	172
Ethnicity Units: Subjects			
African	1	1	2
Caucasian	164	85	249
East Asian	2	0	2
Hispanic	4	5	9
West Asian	3	1	4

End points

End points reporting groups

Reporting group title	500 mg Enzastaurin
Reporting group description:	
500 mg enzastaurin administered daily oral dose (four 125-mg tablets once a day) starting on Day 2 with an 1125-mg loading dose (three 125-mg tablets taken 3 times a day).	
Reporting group title	Lomustine
Reporting group description:	
10 mg, 40 mg, or 100 mg lomustine administered orally as 100 to 130 mg/m2 on Day 1 of each 6-week treatment cycle.	
Subject analysis set title	250 mg Enzastaurin
Subject analysis set type	Full analysis
Subject analysis set description:	
500 mg enzastaurin administered daily.	
Subject analysis set title	High Expresssion Enzastaurin
Subject analysis set type	Full analysis
Subject analysis set description:	
High Expresssion Enzastaurin	
Subject analysis set title	Low Expresssion Enzastaurin
Subject analysis set type	Full analysis
Subject analysis set description:	
Low Expresssion Enzastaurin	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
PFS is the time from the date of randomization to the first evidence of disease progression as defined by response evaluation criteria in solid tumors (RECIST) v1 or death from any cause. Progressive disease (PD) was identified by either a radiologic assessment (MRI) or evidence of neurologic progression. A worsening of the radiologic assessment or neurologic examination findings was presumed evidence of PD. The date on which a participant's disease progressed would be the earlier date derived from radiologic progression or neurologic progression.	
Analysis Population Description: All participants who received at least one dose of drug. Participants censored were: 500 mg Enzastaurin=18 and Lomustine=22.	
End point type	Primary
End point timeframe:	
From Date of Randomization until Disease Progression or Death Due to Any Cause Up To 13 Months	

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	92		
Units: months				
median (confidence interval 95%)	1.51 (1.45 to 2.10)	1.64 (1.48 to 2.79)		

Statistical analyses

Statistical analysis title	Enzastaurin vs Lomustine PFS
Comparison groups	Lomustine v 500 mg Enzastaurin
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.7

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS defined as the time from the date of randomization to the date of death due to any cause. For participants not known to have died as of the data cutoff date, OS will be censored at the last contact date.

Analysis Population Description: All participants who received at least one dose of study drug. Participants censored were: 500 Enzastaurin= 53 and Lomustine= 33.

End point type	Secondary

End point timeframe:

From Date of Randomization until Death Due to Any Cause Up To 16 Months

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	92		
Units: Months				
median (confidence interval 95%)	6.60 (5.22 to 7.75)	7.13 (6.01 to 8.80)		

Statistical analyses

Statistical analysis title	Enzastaurin vs Lomustine OS
Comparison groups	500 mg Enzastaurin v Lomustine

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.65

Secondary: Number of participants Who Achieved Best Overall Tumor Response of Complete Response (CR) or Partial Response (PR) (Objective Response Rates [ORR])

End point title	Number of participants Who Achieved Best Overall Tumor Response of Complete Response (CR) or Partial Response (PR) (Objective Response Rates [ORR])

End point description:

ORR is the percentage of participants with a confirmed CR or PR, as classified by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.0. CR is the disappearance of all target and non-target lesions; PR is a ≥30% decrease in sum of longest diameter of target lesions without new lesion and progression of non-target lesions.

End point type	Secondary

End point timeframe:

From Date of Randomization to Disease Progression or Death Up to 13 Months

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	92		
Units: participants	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of objective tumor response was measured from the date that measurement criteria are first met for an objective tumor response until the first date of objective PD or death from any cause, whichever occurs first. For responders not known to have died or have objective PD as of the data cut-off date, duration of objective response will be censored at the date of the last objective progression-free disease assessment. Progressive disease (PD) was identified by either a radiologic assessment (MRI) or evidence of neurologic progression. A worsening of the radiologic assessment or neurologic examination findings was presumed evidence of PD. The date on which a participant's disease progressed would be the earlier date derived from radiologic progression or neurologic progression.

End point type	Secondary

End point timeframe:

Time of Response to Time of Measured PD or Death Up to 10 Months

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4[1]		
Units: months				
median (confidence interval 95%)	7.87 (6.80 to 9.63)	9999 (2.79 to 9999)		

Notes:

[1] - 9999=Data Not Available (N/A)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration of Patient-reported Functional Assessment of Cancer Therapy – Brain (FACT-Br) Trial Outcome Index (TOI)

End point title	Time to Deterioration of Patient-reported Functional Assessment of Cancer Therapy – Brain (FACT-Br) Trial Outcome Index (TOI)

End point description:

Time to deterioration (TtD) for each participant is defined as a decrease in the TOI score that is at least the minimally important difference, as compared to the participant's baseline score. Time to deterioration is measured from the date of randomization to the first date of a deterioration in the TOI (as defined by a decrease from baseline in the TOI that is at least the minimally important difference) or of death from any cause. For participants who receive subsequent therapy prior to an observation of deterioration, TtD will be censored at the date of initiation of a subsequent therapy. For participants not known to have died or have an observation of deterioration as of the data cut-off date, TtD will be censored at the date of the last deterioration-free assessment.

Analysis Population Description: All randomized participants who had evaluable data. Number of participants censored were: 500 mg Enzastaurin =73 and Lomustine =40.

End point type	Secondary

End point timeframe:

Randomization to the First Date of a Deterioration in the TOI Up To 14 Months

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)	2.27 (1.71 to 3.35)	2.33 (1.94 to 3.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lost productivity: Number of participants employed prior to diagnosis and after last visit

End point title	Lost productivity: Number of participants employed prior to diagnosis and after last visit

End point description:

To describe the burden of disease, work status (retired, part-time, full-time, or not employed) of the participant was assessed.

Analysis Population Description: All participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Prior to Diagnosis Until Last Patient Visit Up To 16 Months

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[2]	90[3]		
Units: percentage of participants				
number (not applicable)				
Employed prior to diagnosis	45.0	46.7		
Retired Prior to diagnosis	35.7	32.2		
Not Employed After Last Visit	31.8	44.4		
Retired after last visit	49.1	40.7		

Notes:

[2] - The small n for "Not Employed After Last Visit" and "Retired after last visit" was 110.

[3] - The small n for "Not Employed After Last Visit" and "Retired after last visit" was 54.

Statistical analyses

No statistical analyses for this end point

Secondary: Assess Biomarkers: PFS by High Protein Expression Level Versus a Low Protein Expression Level

End point title	Assess Biomarkers: PFS by High Protein Expression Level Versus a Low Protein Expression Level

End point description:

Assess Biomarkers: PFS by high protein expression level versus a low protein expression level

End point type	Secondary

End point timeframe:

Prior to Diagnosis Until Last Patient Visit Up To 16 Months

End point values	High Expresssion Enzastaurin	Low Expresssion Enzastaurin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	174[4]	174[5]		
Units: months				
median (confidence interval 95%)				
PKCb2_Cytoplasm (PKCb2_C)	1.45 (1.41 to 1.61)	1.51 (1.41 to 2.73)		
PKCb2_Nucleus (PKCb2_N)	1.41 (1.38 to 1.51)	1.54 (1.41 to 2.73)		
pCREB_Nucleus (pCREB_N)	1.48 (1.41 to 1.61)	1.45 (1.41 to 2.27)		
pGSK3_Cytoplasm (pGSK3_C)	1.45 (1.41 to 2.79)	1.45 (1.41 to 1.54)		
pGSK3_Nucleus (pGSK3_N)	1.41 (1.38 to 2.86)	1.46 (1.41 to 1.54)		
pS6_Cytoplasm (pS6_C)	1.48 (1.41 to 1.61)	1.45 (1.41 to 2.27)		

Notes:

[4] - The small n for biomarkers are: PKCb2_C=55,PKCb2_N=23, pCREB_N=73, pGSK3_C=34, pGSK3_N=27, pS6_C=45

[5] - The small n for biomarkers are: PKCb2_C=41, PKCb2_N=73, pCREB_N=24, pGSK3_C=62, pGSK3_N=69,pS6_C=52

Statistical analyses

Statistical analysis title	PKCb2_Cytoplasm

Statistical analysis description:

There were 174 participants in the enzastaurin arm.
The "subject in this analysis value =348" below in incorrect due to database adding numbers for both cohorts (low expression and high expression) together

Comparison groups	Low Expresssion Enzastaurin v High Expresssion Enzastaurin
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.093

Statistical analysis title	PKCb2_Nucleus

Statistical analysis description:

There were 174 participants in the enzastaurin arm.
The "subject in this analysis value =348" below in incorrect due to database adding numbers for both cohorts (low expression and high expression) together.

Comparison groups	High Expresssion Enzastaurin v Low Expresssion Enzastaurin

Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.007
upper limit	2.704

Statistical analysis title	pCREB_Nucleus

Statistical analysis description:

There were 174 participants in the enzastaurin arm.
The "subject in this analysis value =348" below in incorrect due to database adding numbers for both cohorts (low expression and high expression) together.

Comparison groups	High Expresssion Enzastaurin v Low Expresssion Enzastaurin
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.712
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.436
upper limit	1.162

Statistical analysis title	pGSK3_Cytoplasm

Statistical analysis description:

There were 174 participants in the enzastaurin arm.
The "subject in this analysis value =348" below in incorrect due to database adding numbers for both cohorts (low expression and high expression) together.

Comparison groups	High Expresssion Enzastaurin v Low Expresssion Enzastaurin
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.944
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.611
upper limit	1.46

Statistical analysis title	pGSK3_Nucleus

Statistical analysis description:

There were 174 participants in the enzastaurin arm.
The "subject in this analysis value =348" below in incorrect due to database adding numbers for both cohorts (low expression and high expression) together.

Comparison groups	High Expresssion Enzastaurin v Low Expresssion Enzastaurin
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.946
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.517

Statistical analysis title	pS6_Cytoplasm

Statistical analysis description:

There were 174 participants in the enzastaurin arm.
The "subject in this analysis value =348" below in incorrect due to database adding numbers for both cohorts (low expression and high expression) together.

Comparison groups	High Expresssion Enzastaurin v Low Expresssion Enzastaurin
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.743
upper limit	1.74

Secondary: Number of participants Neurologic Exam Scores by Time

End point title	Number of participants Neurologic Exam Scores by Time

End point description:

Neurologic Function:
0 - No neurologic symptoms; fully active at home/work without assistance.
1 - Minor neurologic symptoms; fully active at home/work without assistance.
2 - Moderate neurologic symptoms; fully active at home/work but requires assistance.
3 -Moderate neurologic symptoms; less than fully active at home/work and requires assistance.

End point type	Secondary

End point timeframe:

Baseline Through 16 Months

End point values	500 mg Enzastaurin	Lomustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	92		
Units: participants				
Number of patients with score <3 at Baseline	119	63		
Number of patients with score <3 at 90 days	100	50		
Number of patients with score <3 at 180 days	43	28		
Number of patients with score >=3 at Baseline	25	14		
Number of patients with score >=3 at 90 days	47	29		
Number of patients with score >=3 at 180 days	17	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) Cycle 1 Day 21

End point title	Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) Cycle 1 Day 21[6]

End point description:

Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss).

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

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: 1 to 5 hours; Day 21: Predose, 3 to 8 hours postdose; Cycle 4, Day 1:Predose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK data was analyzed for Enzastaurin only.

End point values	500 mg Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: nanomole/Liter				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 21: LY317615	291 (± 129)			
Cycle 1 Day 21: LSN326020	514 (± 66)			

Cycle 1 Day 21:Total Analyte (LY317615+ LSN326020)	860 (± 78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) Cycle 4 Day 1

End point title	Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) Cycle 4 Day 1[7]

End point description:

Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) Cycle 4 Day 1.

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

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: 1 to 5 hours; Day 21: Predose, 3 to 8 hours postdose; Cycle 4, Day 1:Predose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK data was analyzed for Enzastaurin only.

End point values	500 mg Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	6[8]			
Units: nanomole/Liter				
geometric mean (geometric coefficient of variation)				
Cycle 4 Day 1: LY317615	152 (± 95)			
Cycle 4 Day 1: LSN326020	437 (± 53)			
Cycle 4 Day 1: Total Analyte (LY317615 +LSN326020)	598 (± 62)			

Notes:

[8] - Cycle 4 Day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) 250 mg Cycle 1 Day 21

End point title	Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) 250 mg Cycle 1 Day 21

End point description:

Pharmacokinetic (PK): Minimum Observed Drug Concentration During a Dosing Interval at Steady State (Cmin,ss) Cycle 1 Day 21.

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

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: 1 to 5 hours; Day 21: Predose, 3 to 8 hours postdose; Cycle 4, Day 1:Predose

End point values	250 mg Enzastaurin			
Subject group type	Subject analysis set			
Number of subjects analysed	1[9]			
Units: nanomole/Liter				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 21: LY317615	109 (± 9999)			
Cycle 1 Day 21: LSN326020	455 (± 9999)			
Cycle 1 Day 21: Total Analyte (LY317615+ LSN32602)	563 (± 9999)			

Notes:

[9] - 9999=Data Not Available (N/A)

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-JCBF	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Lomustine
Reporting group description:	
10 mg, 40 mg, or 100 mg lomustine administered orally as 100 to 130 mg/m2 on Day 1 of each 6-week treatment cycle.	
Reporting group title	Enzastaurin
Reporting group description:	
500 mg enzastaurin administered daily oral dose (four 125-mg tablets once a day) starting on Day 2 with an 1125-mg loading dose (three 125-mg tablets taken 3 times a day).	

Serious adverse events	Lomustine	Enzastaurin	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 83 (28.92%)	56 / 167 (33.53%)	
number of deaths (all causes)	3	10	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour haemorrhage			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
aortic thrombosis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
deep vein thrombosis			
alternative dictionary used:			

MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematoma			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
cyst drainage			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
chest pain			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
general physical health deterioration			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	2 / 83 (2.41%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
oedema peripheral			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
immobile			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (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			
aspiration			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
cough			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
hypoxia			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
laryngeal ulceration			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pharyngolaryngeal pain			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 83 (2.41%)	7 / 167 (4.19%)	
occurrences causally related to treatment / all	0 / 4	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 2	
respiratory failure			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	1 / 83 (1.20%)	4 / 167 (2.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
disorientation			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
mental status changes			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ammonia increased			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
electrocardiogram t wave inversion			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophil count decreased			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
platelet count decreased			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
brain herniation			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
femoral neck fracture			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
radiation injury			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (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 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
angina pectoris			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiopulmonary failure			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
supraventricular tachycardia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
aphasia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
brain oedema			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 83 (2.41%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
cerebral haematoma			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral haemorrhage			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	2 / 2	
convulsion			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 83 (6.02%)	12 / 167 (7.19%)	
occurrences causally related to treatment / all	0 / 9	2 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
coordination abnormal			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
depressed level of consciousness			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysarthria			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

epilepsy				
alternative dictionary used: MedDRA 10.0				
subjects affected / exposed	2 / 83 (2.41%)	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
grand mal convulsion				
alternative dictionary used: MedDRA 10.0				
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 0	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
haemorrhage intracranial				
alternative dictionary used: MedDRA 10.0				
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
headache				
alternative dictionary used: MedDRA 10.0				
subjects affected / exposed	2 / 83 (2.41%)	3 / 167 (1.80%)		
occurrences causally related to treatment / all	0 / 5	0 / 5		
deaths causally related to treatment / all	0 / 0	0 / 0		
hemiparesis				
alternative dictionary used: MedDRA 10.0				
subjects affected / exposed	0 / 83 (0.00%)	3 / 167 (1.80%)		
occurrences causally related to treatment / all	0 / 0	0 / 8		
deaths causally related to treatment / all	0 / 0	0 / 0		
intracranial pressure increased				
alternative dictionary used: MedDRA 10.0				
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
loss of consciousness				
alternative dictionary used: MedDRA 10.0				

subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
motor dysfunction			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
neurological symptom			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
partial seizures			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
postictal paralysis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
sensorimotor disorder			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
sensory loss			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

somnolence			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
status epilepticus			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
febrile neutropenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	3 / 83 (3.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	3 / 83 (3.61%)	4 / 167 (2.40%)	
occurrences causally related to treatment / all	7 / 7	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal haematoma			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal fistula			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysphagia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
faecal incontinence			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

oesophagitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
stomatitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
angioneurotic oedema			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
urinary incontinence			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscular weakness			

alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
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 10.0			
subjects affected / exposed	3 / 83 (3.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
encephalitis herpes			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
erysipelas			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
escherichia infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal fungal infection			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower respiratory tract infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
meningitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
meningitis bacterial			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 83 (2.41%)	4 / 167 (2.40%)	
occurrences causally related to treatment / all	1 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
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 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
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 10.0			
subjects affected / exposed	0 / 83 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
diabetes mellitus			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycaemia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	5 / 167 (2.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lomustine	Enzastaurin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 83 (79.52%)	134 / 167 (80.24%)	
Investigations			
haemoglobin decreased			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 83 (6.02%)	4 / 167 (2.40%)	
occurrences (all)	20	15	
neutrophil count decreased			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 83 (6.02%)	1 / 167 (0.60%)	
occurrences (all)	10	4	
Injury, poisoning and procedural complications			
contusion			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 83 (2.41%)	10 / 167 (5.99%)	
occurrences (all)	6	35	
Nervous system disorders			

convulsion			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	6 / 83 (7.23%)	16 / 167 (9.58%)	
occurrences (all)	17	37	
headache			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	16 / 83 (19.28%)	31 / 167 (18.56%)	
occurrences (all)	50	78	
hemiparesis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	6 / 83 (7.23%)	4 / 167 (2.40%)	
occurrences (all)	21	10	
memory impairment			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 83 (6.02%)	8 / 167 (4.79%)	
occurrences (all)	25	26	
somnolence			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	11 / 167 (6.59%)	
occurrences (all)	3	22	
speech disorder			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	6 / 83 (7.23%)	12 / 167 (7.19%)	
occurrences (all)	14	38	
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	20 / 83 (24.10%)	26 / 167 (15.57%)	
occurrences (all)	67	84	
oedema peripheral			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	7 / 83 (8.43%)	18 / 167 (10.78%)	
occurrences (all)	26	57	
Blood and lymphatic system disorders			

leukopenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	10 / 83 (12.05%)	3 / 167 (1.80%)	
occurrences (all)	25	6	
neutropenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	15 / 83 (18.07%)	0 / 167 (0.00%)	
occurrences (all)	32	0	
thrombocytopenia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	35 / 83 (42.17%)	11 / 167 (6.59%)	
occurrences (all)	98	24	
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 83 (6.02%)	16 / 167 (9.58%)	
occurrences (all)	8	44	
diarrhoea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	4 / 83 (4.82%)	14 / 167 (8.38%)	
occurrences (all)	6	32	
faeces discoloured			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 83 (0.00%)	9 / 167 (5.39%)	
occurrences (all)	0	32	
nausea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	18 / 83 (21.69%)	18 / 167 (10.78%)	
occurrences (all)	37	33	
vomiting			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	6 / 83 (7.23%)	14 / 167 (8.38%)	
occurrences (all)	6	22	
Respiratory, thoracic and mediastinal disorders			

cough			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	3 / 83 (3.61%)	10 / 167 (5.99%)	
occurrences (all)	7	23	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 83 (1.20%)	10 / 167 (5.99%)	
occurrences (all)	3	26	
confusional state			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	10 / 83 (12.05%)	16 / 167 (9.58%)	
occurrences (all)	23	30	
depression			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 83 (6.02%)	3 / 167 (1.80%)	
occurrences (all)	17	10	
insomnia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	6 / 83 (7.23%)	8 / 167 (4.79%)	
occurrences (all)	20	21	
Renal and urinary disorders			
urinary incontinence			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	6 / 83 (7.23%)	7 / 167 (4.19%)	
occurrences (all)	14	15	
Musculoskeletal and connective tissue disorders			
muscular weakness			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	7 / 83 (8.43%)	14 / 167 (8.38%)	
occurrences (all)	24	74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated due to futility.

Notes: