Clinical trial results:
A Phase 2 Study of Enzastaurin in Participants with Follicular Lymphoma

Summary

EudraCT number	2007-006246-17
Trial protocol	DE
Global end of trial date	31 March 2015

Results information

Result version number	v1 (current)
This version publication date	15 September 2018
First version publication date	15 September 2018

Trial information

Trial identification

Sponsor protocol code	H6Q-MC-S011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00475644
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 8671

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Country Code 1, Telephone 877CTLilly, 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	11 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity, as measured by tumor response rate, of enzastaurin in participants with Follicular Lymphoma (FL).

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	11 May 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	66
EEA total number of subjects	20

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)	40
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who were considered to have completed the study who received at least 1 dose of study drug, did not have any protocol violations, and from whom a valid assay result was obtained.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Enzastaurin

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	LY317615
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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

Number of subjects in period 1	Enzastaurin
Started	66
Received at Least One Dose of Study Drug	66
Completed	53
Not completed	13
Protocol deviation	13

Baseline characteristics

Reporting groups	
Reporting group title	Enzastaurin
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 values	Enzastaurin	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	26	26	
85 years and over	0	0	
Gender, Male/Female Units:			
Male	43	43	
Female	23	23	

End points

End points reporting groups

Reporting group title	Enzastaurin

Reporting group description:

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

Primary: Tumor Response Rate (RR) (Percentage of Participants Exhibiting Complete Response [CR] or Complete Response Unconfirmed [CRu] or Partial Response [PR])

End point title	Tumor Response Rate (RR) (Percentage of Participants Exhibiting Complete Response [CR] or Complete Response Unconfirmed [CRu] or Partial Response [PR])[1]

End point description:

Tumor response rate is defined as the number of responders divided by the number of treated patients. A responder is a patient who exhibits a complete response (CR), complete response unconfirmed (CRu), or partial response (PR) as defined by Cheson et al. (1999). CR, the disappearance of target lesions and any pathological lymph nodes [target or non-target] taking as reference the baseline sum of diameters in response to treatment; CRu, complete disappearance of all detectable clinical and radiographic evidence of disease, return of spleen to non-palpable if involved, residual lymph node mass greater than 1.5 centimeters (cm) has regressed by more than 75%; PR, 50% decrease in the sum of the products of the greatest diameter (SPD) of the 6 largest dominant masses, no increase of other nodes, liver or spleen and no new sites of disease.

End point type	Primary

End point timeframe:

Baseline to Measured Progressive Disease (up to 1559 Days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study with no comparison groups.

End point values	Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	53[2]			
Units: percentage of participants				
number (confidence interval 95%)	26.4 (15.3 to 40.3)			

Notes:

[2] - Participants who received at least 1 dose of study drug and did not violate any study criteria.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free survival (PFS)

End point title	Progression-Free survival (PFS)

End point description:

PFS is defined as the time from the date of study enrollment to the first date of measured progressive disease or death from any cause. For patients not known to have died as of the data cut-off date and who do not have objective progressive disease, PFS will be censored at the date of the last objective progression-free assessment. For patients who receive subsequent anticancer therapy (after discontinuation from the study treatment) prior to objective disease progression or death, PFS will be

censored at the date of last objective progression-free assessment prior to the initiation of postdiscontinuation anticancer therapy. For reference, PFS will also be calculated and analyzed based on an alternative definition of censoring: for each patient who is not known to have died or to have had objective progression of disease as of the data cut-off date, PFS will be censored for that analysis at the date of last prior contact.

End point type	Secondary

End point timeframe:

Baseline to Measured Progressive Disease or Death from Any Cause (Up to 1559 Days)

End point values	Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	53[3]			
Units: Days				
median (confidence interval 95%)	551.0 (350.0 to 863.0)			

Notes:

[3] - Participants who received at least 1 dose of study drug and did not violate any study criteria.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TtR)

End point title	Time to response (TtR)

End point description:

TtR is defined as the time from the date of study enrollment to the date of response (CR, CRu, or PR) for patients who have responded prior to receiving any subsequent anticancer therapy.CR, the disappearance of target lesions and any pathological lymph nodes [target or non-target] taking as reference the baseline sum of diameters in response to treatment; CRu, complete disappearance of all detectable clinical and radiographic evidence of disease, return of spleen to non-palpable if involved, residual lymph node mass greater than 1.5 centimeters (cm) has regressed by more than 75%; PR, 50% decrease in the sum of the products of the greatest diameter (SPD) of the 6 largest dominant masses, no increase of other nodes, liver or spleen and no new sites of disease.

End point type	Secondary

End point timeframe:

Baseline to Date of Confirmed Response (Up to 890 Days)

End point values	Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	14[4]			
Units: Days				
median (confidence interval 95%)	148.0 (84.0 to 246.0)			

Notes:

[4] - Participants who received study drug and had a baseline and post-baseline response.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR)

End point title	Duration of response (DoR)

End point description:

DoR is defined as the time from the date when the measurement criteria are met for CR, CRu, or PR (whichever status is recorded first) until the date of first observation of measured progressive disease. For responding patients who die without progressive disease (including death from study disease), DoR will be censored at the date of death. For responding patients not known to have died as of the data cut-off date and who do not have progressive disease, DoR will be censored at the last objective progression-free assessment date prior to the data cut-off date. For responding patients who receive subsequent anticancer therapy (after discontinuation from the study treatment) prior to disease progression, DoR will be censored at the date of last objective progression-free assessment prior to the initiation of postdiscontinuation anticancer therapy.

End point type	Secondary

End point timeframe:

Time of Response to Measured Progressive Disease (Up to 1415 Days)

End point values	Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	14[5]			
Units: Days				
median (confidence interval 95%)	604.8 (419.2 to 790.4)			

Notes:

[5] - All participants who receive 1 dose of study drug,did not violate study criteria and had a response.

Statistical analyses

No statistical analyses for this end point

Secondary: RR (Response Rate) of Participants with Expression of Protein Biomarkers

End point title	RR (Response Rate) of Participants with Expression of Protein Biomarkers

End point description:

Correlative analyses of tumor RR for PKC-β2 (protein kinase C-β) protein expression. Immunohistochemistry (IHC) staining was performed to assess protein expression of PKC-β2 in cytoplasm reported as H scores (logistic model of response rate), which was derived from a weighted average of staining intensity (scale 0 to 3, increasing intensity) and percentage of positive cells (0 to 100%) at each staining intensity. PKC-β2 expression was further classified into high vs. low expression using the cutpoint of the median of the distribution of PKC-β2 H scores. This is an odds ratio for better tumor response comparing high to low biomarker expression levels.

End point type	Secondary

End point timeframe:

Baseline

End point values	Enzastaurin			
Subject group type	Reporting group			
Number of subjects analysed	12[6]			
Units: biomarker expression				
median (confidence interval 95%)	0.031 (0.001 to 0.860)			

Notes:

[6] - The Translational Research population consisted of participants from whom tumor tissue was obtained.

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:

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Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Enzastaurin

Reporting group description: -

Serious adverse events	Enzastaurin		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 66 (24.24%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
prostate cancer			
subjects affected / exposed[1]	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
rectal adenoma			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

ankle fracture				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
femur fracture				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
fractured sacrum				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
incisional hernia				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
deep vein thrombosis				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
angina pectoris				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
palpitations				
alternative dictionary used: MedDRA 12.0				

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
visual acuity reduced			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pancreatitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
pancreatitis acute			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
cholelithiasis				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
dyspnoea				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
pulmonary embolism				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
mental status changes				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
renal mass				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
bronchitis				
alternative dictionary used: MedDRA 12.0				

subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
sepsis				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
dehydration				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
failure to thrive				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
hypertriglyceridaemia				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
hypokalaemia				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 66 (1.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	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.

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

Non-serious adverse events	Enzastaurin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 66 (93.94%)		
Cardiac disorders			
palpitations			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	19		
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	8 / 66 (12.12%)		
occurrences (all)	50		
headache			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	11 / 66 (16.67%)		
occurrences (all)	69		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	9 / 66 (13.64%)		
occurrences (all)	36		
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	25 / 66 (37.88%)		
occurrences (all)	139		
oedema peripheral			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	6 / 66 (9.09%)		
occurrences (all)	26		
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	29		

abdominal pain				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	8 / 66 (12.12%)			
occurrences (all)	22			
abdominal pain upper				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	5 / 66 (7.58%)			
occurrences (all)	22			
constipation				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	10 / 66 (15.15%)			
occurrences (all)	53			
diarrhoea				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	20 / 66 (30.30%)			
occurrences (all)	121			
dyspepsia				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	6 / 66 (9.09%)			
occurrences (all)	38			
faeces discoloured				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	10 / 66 (15.15%)			
occurrences (all)	91			
flatulence				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	5 / 66 (7.58%)			
occurrences (all)	21			
nausea				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	19 / 66 (28.79%)			
occurrences (all)	77			
stomatitis				
alternative dictionary used: MedDRA 12.0				

subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	12		
vomiting			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	13 / 66 (19.70%)		
occurrences (all)	36		
dyspnoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	8 / 66 (12.12%)		
occurrences (all)	43		
oropharyngeal pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
dry skin			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	26		
hyperhidrosis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	21		
night sweats			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	8 / 66 (12.12%)		
occurrences (all)	36		
rash			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	6 / 66 (9.09%)		
occurrences (all)	27		
rash pruritic			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	10		
Renal and urinary disorders			
chromaturia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	14 / 66 (21.21%)		
occurrences (all)	114		
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	34		
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	11 / 66 (16.67%)		
occurrences (all)	56		
back pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	9 / 66 (13.64%)		
occurrences (all)	44		
musculoskeletal pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	22		
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	12		
oral herpes			

alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	13		
rhinitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	5		
sinusitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	11		
upper respiratory tract infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	10		
urinary tract infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	10		

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

None reported