Clinical trial results:
A Randomized Phase 2 Study of Pemetrexed in Combination with Cisplatin or Carboplatin as Adjuvant Chemotherapy in Patients with Completely Resected Stage Ib or II Non-Small Cell Lung Cancer

Summary

EudraCT number	2005-002911-26
Trial protocol	DE ES
Global end of trial date	30 July 2013

Results information

Result version number	v1 (current)
This version publication date	04 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	H3E-SB-S089

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00269152
WHO universal trial number (UTN)	-
Other trial identifiers	Trial ID: 10105, Trial Alias: H3E-SB-S089

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, 1 800-285-4559,

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

Global end of trial reached?	Yes
Global end of trial date	30 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is a multicenter, open-label, two-arm, randomized, parallel Phase 2 feasibility study of pemetrexed in combination with either cisplatin (Arm A) or carboplatin (Arm B) as adjuvant combination-chemotherapy in participants with completely resected, stage Ib or IIa/IIb non-small cell lung cancer (NSCLC).
A two-stage design will be employed independently for both treatment arms, with the possibility of stopping each treatment early for lack of feasibility.

Protection of trial subjects:

This study was conducted in accordance with International Code of 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	21 December 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 87
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	France: 20
Worldwide total number of subjects	122
EEA total number of subjects	122

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	82
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Not Applicable

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	Pemetrexed + Cisplatin

Arm description:

Pemetrexed: 500 milligrams per square meter (mg/m^2), intravenous (IV), every 21 days x 4 cycles
Cisplatin: 75 mg/m^2, intravenous (IV), every 21 days x 4 cycles

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY213514, Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed: 500 milligrams per square meter (mg/m^2), intravenous (IV), every 21 days x 4 cycles

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin: 75 mg/m^2, intravenous (IV), every 21 days x 4 cycles

Arm title	Pemetrexed + Carboplatin

Arm description:

Pemetrexed: 500 mg/m^2, intravenous (IV), every 21 days x 4 cycles
Carboplatin: area under the curve (AUC) 5 milligrams per milliliter*minute (mg/ml*min), intravenous (IV), every 21 days x 4 cycles

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY213514, Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed: 500 mg/m^2, intravenous (IV), every 21 days x 4 cycles

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin: area under the curve (AUC) 5 milligrams per milliliter*minute (mg/ml*min), intravenous (IV), every 21 days x 4 cycles

Number of subjects in period 1	Pemetrexed + Cisplatin	Pemetrexed + Carboplatin
Started	63	59
Completed	45	49
Not completed	18	10
Physician decision	2	3
Adverse event, non-fatal	9	3
Protocol violation	-	1
Withdrawal by subject	7	3

Baseline characteristics

Reporting groups	
Reporting group title	Pemetrexed + Cisplatin
Reporting group description:	
Pemetrexed: 500 milligrams per square meter (mg/m^2), intravenous (IV), every 21 days x 4 cycles Cisplatin: 75 mg/m^2, intravenous (IV), every 21 days x 4 cycles	
Reporting group title	Pemetrexed + Carboplatin
Reporting group description:	
Pemetrexed: 500 mg/m^2, intravenous (IV), every 21 days x 4 cycles Carboplatin: area under the curve (AUC) 5 milligrams per milliliter*minute (mg/ml*min), intravenous (IV), every 21 days x 4 cycles	

Reporting group values	Pemetrexed + Cisplatin	Pemetrexed + Carboplatin	Total
Number of subjects	63	59	122
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	60.6	58.9	
standard deviation	± 7.7	± 7.2	-
Gender, Male/Female Units: participants			
Female	14	18	32
Male	49	41	90
Race, Customized Units: Subjects			
Caucasian	62	58	120
African	1	1	2
Region of Enrollment Units: Subjects			
France	12	8	20
Spain	7	8	15
Germany	44	43	87
Curative Surgery Used Units: Subjects			
Pneumonectomy	9	9	18
Lobectomy	46	46	92
Bi-lobectomy	8	4	12
Smoking History Units: Subjects			
Yes	56	56	112
No	7	3	10
Stage of Disease Prior to Tumor Resection			
Classification based on the American Joint Committee on Cancer Staging Criteria for Lung Cancer.			
Units: Subjects			
Stage Ia	0	1	1

Stage Ib	27	26	53
Stage IIa	6	5	11
Stage IIb	30	25	55
Stage IIIa	0	1	1
Unknown: could have been either Stage IIIb or IV	0	1	1
Tumor Type at Initial Pathological Diagnosis Units: Subjects			
Adenocarcinoma of the Lung	27	23	50
Squamous Carcinoma of the Lung	24	20	44
Non-Small Cell Lung Cancer	5	4	9
Mixed Cell (Squamous/Adeno) Carcinoma of Lung	0	5	5
Large Cell Carcinoma of Lung	5	7	12
Bronchoalveolar Carcinoma	2	0	2

End points

End points reporting groups

Reporting group title	Pemetrexed + Cisplatin
Reporting group description:	
Pemetrexed: 500 milligrams per square meter (mg/m^2), intravenous (IV), every 21 days x 4 cycles Cisplatin: 75 mg/m^2, intravenous (IV), every 21 days x 4 cycles	
Reporting group title	Pemetrexed + Carboplatin
Reporting group description:	
Pemetrexed: 500 mg/m^2, intravenous (IV), every 21 days x 4 cycles Carboplatin: area under the curve (AUC) 5 milligrams per milliliter*minute (mg/ml*min), intravenous (IV), every 21 days x 4 cycles	
Subject analysis set title	Pemetrexed+Cisplatin (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
1 patient randomized to pemetrexed+carboplatin was accidentally treated with pemetrexed+cisplatin. This patient was analyzed for efficacy as randomized and for safety as treated.	

Primary: The Feasibility of Adjuvant Chemotherapy

End point title	The Feasibility of Adjuvant Chemotherapy[1][2]
End point description:	
The purpose of the study was to determine the feasibility rate of the treatment regimen. The treatment was considered feasible if the participant was able to complete 4 cycles of chemotherapy as defined by the protocol, was alive, and showed no Grade 3 toxicities at the follow-up visit 30 days after the last infusion of study drugs.	
End point type	Primary
End point timeframe:	
every 21-day cycle for 4 cycles up to 30 days after last infusion	

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: Unable to provide statistical analysis for single reporting group with no comparison group due to system limitations in EudraCT database.
[2] - 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: Unable to provide statistical analysis for single reporting group with no comparison group due to system limitations in EudraCT database.

End point values	Pemetrexed + Carboplatin	Pemetrexed+Cisplatin (Safety)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	54	64		
Units: participants				
number (not applicable)				
Participants "feasible"	27	38		
Non-feasible = Early Discontinuation	6	18		
Non-feasible = Lost to Follow-up	2	1		
Non-feasible = Remaining Grade 3/4 Toxicity	3	4		
Non-feasible = Underdosage (<95% intended dose)	19	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Grade III/IV Adverse Events

End point title	Grade III/IV Adverse Events[3]

End point description:

Number of participants experiencing Grade III/IV hematologic and non-hematologic adverse events possibly related to study drug or protocol procedures in this study.

End point type	Secondary

End point timeframe:

every 21-day cycle for 4 cycles

Notes:

[3] - 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: Unable to provide statistical analysis for single reporting group with no comparison group due to system limitations in EudraCT database.

End point values	Pemetrexed + Carboplatin	Pemetrexed+Cisplatin (Safety)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	54	64		
Units: participants				
number (not applicable)				
Neutropenia	6	9		
Anaemia	3	0		
Thrombocytopenia	3	0		
Febrile neutropenia	2	0		
Leukopenia	1	0		
Lymphopenia	0	1		
Neutrophil count decreased	6	1		
Haemoglobin count decreased	2	0		
Platelet count decreased	1	1		
White blood cell count decreased	2	0		
Asthenia	2	4		
Nausea	0	3		
Vomiting	0	3		
Fatigue	2	0		
Catheter related infection	0	1		
Gamma-glutamyltransferase increased	0	1		
Anorexia	0	1		
Hyperglycaemia	0	1		
Hyperkalaemia	0	1		
Psychotic disorder	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 3 Years

End point title	Overall Survival at 3 Years

End point description:

For each treatment arm, the Kaplan-Meier technique was used to estimate the 3 year survival rate. Results are presented as probability (%) of survival at 3 years. Overall survival is the duration from enrollment to death. For participants not known to have died, overall survival was censored at the last known alive date.

End point type	Secondary

End point timeframe:

baseline to date of death from any cause, assessed at 3 years

End point values	Pemetrexed + Cisplatin	Pemetrexed + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	59		
Units: percent probability of survival (%)				
number (confidence interval 95%)	82 (72.4 to 91.6)	83.2 (73.2 to 93.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3 Year Disease-Free Survival: Probability of Disease-Free Survival at 3 Years

End point title	3 Year Disease-Free Survival: Probability of Disease-Free Survival at 3 Years

End point description:

For each treatment arm, the Kaplan-Meier technique was used to estimate the 3 year disease-free rate. Disease-free survival is defined as the time from enrollment to the first observation of disease progression, or death due to any cause. For participants not known to have died and to have had recurrent disease, disease-free survival was censored at the date of the last participant contact with No Recurrence status. Results are presented as probability (%) of disease-free survival at 3 years.

End point type	Secondary

End point timeframe:

length of time disease free, assessed at 3 years

End point values	Pemetrexed + Cisplatin	Pemetrexed + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	59		
Units: probability of disease-free survival (%)				
number (confidence interval 95%)	61.2 (48.3 to 74)	67.3 (54.5 to 80.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 6 Years

End point title	Overall Survival at 6 Years

End point description:

For each treatment arm, the Kaplan-Meier technique was used to estimate the 6 year survival rate. Results are presented as probability (%) of survival at 6 years. Overall survival is the duration from enrollment to death. For participants not known to have died, overall survival was censored at the last known alive date.

End point type	Secondary

End point timeframe:

Baseline to date of death from any cause assessed at 6 years

End point values	Pemetrexed + Cisplatin	Pemetrexed + Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	59		
Units: percent probability of survival (%)				
number (confidence interval 95%)	72.6 (59.3 to 85.9)	83.2 (73.2 to 93.2)		

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:

H3E-SB-S089

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	Pemetrexed and Carboplatin
Reporting group description: -	
Reporting group title	Pemetrexed and Cisplatin

Reporting group description: -

Serious adverse events	Pemetrexed and Carboplatin	Pemetrexed and Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 54 (9.26%)	19 / 64 (29.69%)	
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)			
cancer pain			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
aortic aneurysm			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral ischaemia			
alternative dictionary used: MedDRA 8.1			

subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial flutter			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute myocardial infarction			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tachyarrhythmia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebrovascular accident			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
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			
chest pain			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
febrile neutropenia			
alternative dictionary used: MedDRA 8.1			

subjects affected / exposed	2 / 54 (3.70%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
visual disturbance			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	4 / 64 (6.25%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
splenic artery aneurysm			
alternative dictionary used: MedDRA 8.1			

subjects affected / exposed	1 / 54 (1.85%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal haemorrhage			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
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 8.1			
subjects affected / exposed	0 / 54 (0.00%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	5 / 64 (7.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
psychotic disorder			
alternative dictionary used: MedDRA 8.1			

subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
restlessness			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	1 / 54 (1.85%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
catheter related infection			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
erysipelas			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection			
alternative dictionary used: MedDRA 8.1			

subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
anorexia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperkalaemia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 64 (1.56%)	
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	Pemetrexed and Carboplatin	Pemetrexed and Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 54 (92.59%)	59 / 64 (92.19%)	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	13 / 54 (24.07%)	10 / 64 (15.63%)	
occurrences (all)	15	22	
chest pain			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	4 / 54 (7.41%)	3 / 64 (4.69%)	
occurrences (all)	6	3	
fatigue			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	21 / 54 (38.89%)	23 / 64 (35.94%)	
occurrences (all)	25	40	
mucosal inflammation			

alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	2 / 54 (3.70%)	6 / 64 (9.38%)	
occurrences (all)	2	7	
pyrexia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	3 / 64 (4.69%)	
occurrences (all)	4	3	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	16 / 54 (29.63%)	6 / 64 (9.38%)	
occurrences (all)	19	7	
epistaxis			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	4 / 54 (7.41%)	2 / 64 (3.13%)	
occurrences (all)	6	2	
dyspnoea			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	9 / 54 (16.67%)	7 / 64 (10.94%)	
occurrences (all)	10	8	
Psychiatric disorders			
sleep disorder			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	4 / 54 (7.41%)	4 / 64 (6.25%)	
occurrences (all)	4	6	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	6 / 54 (11.11%)	0 / 64 (0.00%)	
occurrences (all)	8	0	
haemoglobin decreased			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	6 / 54 (11.11%)	2 / 64 (3.13%)	
occurrences (all)	11	2	
neutrophil count decreased			

alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	10 / 54 (18.52%)	4 / 64 (6.25%)	
occurrences (all)	22	11	
platelet count decreased			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	10 / 54 (18.52%)	4 / 64 (6.25%)	
occurrences (all)	16	9	
weight decreased			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	3 / 64 (4.69%)	
occurrences (all)	3	5	
white blood cell count decreased			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	9 / 54 (16.67%)	2 / 64 (3.13%)	
occurrences (all)	17	4	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	4 / 64 (6.25%)	
occurrences (all)	3	5	
dysgeusia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	7 / 54 (12.96%)	3 / 64 (4.69%)	
occurrences (all)	9	4	
headache			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	6 / 54 (11.11%)	8 / 64 (12.50%)	
occurrences (all)	8	12	
paraesthesia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	4 / 54 (7.41%)	3 / 64 (4.69%)	
occurrences (all)	4	3	
Blood and lymphatic system disorders			

anaemia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	8 / 54 (14.81%)	12 / 64 (18.75%)	
occurrences (all)	9	14	
neutropenia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	15 / 54 (27.78%)	21 / 64 (32.81%)	
occurrences (all)	36	34	
leukopenia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	5 / 64 (7.81%)	
occurrences (all)	4	8	
thrombocytopenia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	7 / 54 (12.96%)	3 / 64 (4.69%)	
occurrences (all)	12	3	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Eye disorders			
conjunctivitis			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	6 / 54 (11.11%)	1 / 64 (1.56%)	
occurrences (all)	7	1	
lacrimation increased			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	2 / 64 (3.13%)	
occurrences (all)	3	3	
keratoconjunctivitis sicca			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 64 (1.56%)	
occurrences (all)	3	3	
Gastrointestinal disorders			

abdominal pain upper			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	5 / 54 (9.26%)	6 / 64 (9.38%)	
occurrences (all)	6	7	
diarrhoea			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	7 / 54 (12.96%)	5 / 64 (7.81%)	
occurrences (all)	11	7	
constipation			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	8 / 54 (14.81%)	17 / 64 (26.56%)	
occurrences (all)	10	30	
dyspepsia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	2 / 54 (3.70%)	4 / 64 (6.25%)	
occurrences (all)	4	5	
dysphagia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	2 / 64 (3.13%)	
occurrences (all)	3	2	
nausea			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	30 / 54 (55.56%)	40 / 64 (62.50%)	
occurrences (all)	60	82	
stomatitis			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	5 / 54 (9.26%)	3 / 64 (4.69%)	
occurrences (all)	7	4	
vomiting			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	17 / 54 (31.48%)	21 / 64 (32.81%)	
occurrences (all)	24	31	
Skin and subcutaneous tissue disorders			

alopecia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	5 / 54 (9.26%)	4 / 64 (6.25%)	
occurrences (all)	5	4	
pruritus			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
rash			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	4 / 54 (7.41%)	2 / 64 (3.13%)	
occurrences (all)	4	3	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	1 / 54 (1.85%)	4 / 64 (6.25%)	
occurrences (all)	1	4	
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	4 / 54 (7.41%)	2 / 64 (3.13%)	
occurrences (all)	5	2	
Metabolism and nutrition disorders			
anorexia			
alternative dictionary used: MedDRA 8.1			
subjects affected / exposed	14 / 54 (25.93%)	10 / 64 (15.63%)	
occurrences (all)	19	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2011	A protocol amendment after the trial original completed to allow for additional 3 years for collection of additional overall survival data due to number of participants surviving at 3 years. Long-term survival follow-up was increased by this amendment to 6 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 March 2008	The protocol was amended to extend the long-term follow-up period to 6 years to allow for collection of additional overall survival data.	30 May 2011

Notes:

Limitations and caveats

None reported