Clinical trial results:
A Phase 2 Study to Evaluate LY2603618 in Combination with Pemetrexed in Patients with Advanced or Metastatic Non-small Cell Lung Cancer

Summary

EudraCT number	2009-013787-39
Trial protocol	IT
Global end of trial date	11 November 2014

Results information

Result version number	v1 (current)
This version publication date	30 July 2017
First version publication date	30 July 2017

Trial information

Trial identification

Sponsor protocol code	I2I-MC-JMMD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00988858
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 12092

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 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to evaluate the efficacy and safety of LY2603618 in combination with pemetrexed and any side effects that might be associated with it along with determining the effects of LY2603618 in combination with pemetrexed in participants with advanced or metastatic Non-small Cell Lung Cancer (NSCLC).

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	12 November 2009
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	United States: 24
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	55
EEA total number of subjects	12

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)	32
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants that had progressive disease were completers.

Period 1

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

Arms

Arm title	LY2603618 and Pemetrexed

Arm description:

LY2603618: 150 milligram per square meter mg/m^2 intravenously on Day 2 of each 21 day cycle repeating every 21 days for a planned minimum of 2 cycles or until disease progression

Pemetrexed: 500mg/m^2 intravenously on Day 1 of each 21 Day cycle repeating every 21 days for a planned minimum of 2 cycles or until disease progression

Arm type	Experimental
Investigational medicinal product name	LY2603618
Investigational medicinal product code	
Other name	CHK-1 Inhibitor I
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

150 milligram per square meter (mg/m^2) intravenously on Day 2 of each 21 day cycle repeating every 21 days for a planned minimum of 2 cycles continuing until disease progression

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m^2 intravenously on Day 1 of each 21 Day cycle repeating every 21 days for a planned minimum of 2 cycles or until disease progression

Number of subjects in period 1	LY2603618 and Pemetrexed
Started	55
Completed	45
Not completed	10
Physician decision	1
Adverse event, non-fatal	7
Death	1

Sponsor Decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	55	55	
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 Units: years			
arithmetic mean	61.2		
standard deviation	± 8.6	-	
Gender, Male/Female Units:			
Male	34	34	
Female	21	21	
Region of Enrollment Units: Subjects			
United States	24	24	
Taiwan	5	5	
Korea, Republic of	14	14	
Italy	12	12	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	55	55	
Unknown or Not Reported	0	0	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	21	21	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	33	33	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	LY2603618 and Pemetrexed

Reporting group description:

LY2603618: 150 milligram per square meter mg/m^2 intravenously on Day 2 of each 21 day cycle repeating every 21 days for a planned minimum of 2 cycles or until disease progression

Pemetrexed: 500mg/m^2 intravenously on Day 1 of each 21 Day cycle repeating every 21 days for a planned minimum of 2 cycles or until disease progression

Primary: Overall Tumor Response - Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) [Overall Response Rate (ORR)]

End point title	Overall Tumor Response - Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) [Overall Response Rate (ORR)][1]

End point description:

Overall response rate is the best response of complete response (CR) or partial response (PR) as classified by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST v1.1). CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of not-target lesions or appearance of new lesions. Overall response rate is calculated as a total number of participants with CR or PR divided by the total number of participants with at least 1 measurable lesion, multiplied by 100.

Analysis Population Description : All randomized participants who received at least 1 dose of drug.

End point type	Primary

End point timeframe:

Baseline until Progressive Disease or Study Discontinuation (Up to 23 Months)

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 therefore statistical analyses (comparison analysis) were not conducted.

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percentage of participants				
number (confidence interval 95%)	9.1 (3.7 to 18.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS) time was defined as the time from the date of randomization to the first date of progressive disease (symptomatic or objective) or death due to any cause, whichever occurred

first. For participants who were not known to have died or progressed as of the data-inclusion cutoff date, PFS time was censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy. PFS was summarized using Kaplan-Meier estimates.

Analysis Population Description : All randomized participants who received at least 1 dose of drug. 9 participants were censored.

End point type	Secondary

End point timeframe:

Baseline to Progressive Disease or Death Due to Any Cause (Up to 27.1 Months)

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: months				
median (confidence interval 90%)	2.3 (1.4 to 3.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved a Best Response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD) (Clinical Benefit Rate)

End point title	Percentage of Participants Who Achieved a Best Response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD) (Clinical Benefit Rate)

End point description:

Clinical benefit rate is the best response CR, PR, or stable disease (SD) as classified by the investigators according to the RECIST v1.1. CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of not-target lesions or appearance of new lesions. SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since treatment started. Clinical benefit rate is calculated as a total number of participants with CR, PR, or SD divided by the total number of participants with at least 1 measurable lesion, multiplied by 100.

Analysis Population Description : All randomized participants who received at least 1 dose of drug.

End point type	Secondary

End point timeframe:

Baseline until Progressive Disease or Study Discontinuation (Up to 23 Months)

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percentage of participants				
number (confidence interval 90%)	45.5 (33.9 to 57.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Symptom Burden Scores of Lung Cancer Symptom Scale (LCSS)

End point title	Change in Symptom Burden Scores of Lung Cancer Symptom Scale (LCSS)

End point description:

The LCSS participants scale is a 9-item questionnaire. Six questions are symptom-specific measures for lung cancer (appetite, fatigue, cough, dyspnea, hemoptysis and pain), and 3 summation items describe total symptomatic distress, activity status, and overall quality of life. Participant responses were measured using visual analogue scales (VAS) with 100-milliliter (mm) lines. Scores range from 0 (for best outcome) to 100 (for worst outcome). The Average Symptom Burden Index (ASBI) was calculated as the mean of 6 symptom-specific questions from the LCSS.

Analysis Population Description: The LCSS evaluable population consisted of all enrolled participants who had a baseline LCSS measurement and at least 1 post-baseline measurement. The population was evaluated for changes in the ASBI (improved, stable, worsened), with improvement/worsening based on trends seen in sets of consecutive ASBI assessments with respect to baseline ASBI.

End point type	Secondary

End point timeframe:

Baseline until End of Study (Up to 27.1 Months)

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: participants				
number (not applicable)				
Improved	12			
Worsened	6			
Stable	18			
Unknown	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response is defined as the time from the first observation of CR or PR to the first observation of progressive disease (PD) or death from any cause. A response is defined as a confirmed objective status of CR or PR. For participants who are not known to have died as of the data inclusion cut-off date and who do not have PD, the duration will be censored at the date of the last objective progression free disease assessment prior to the date of any subsequent anticancer therapy.

Analysis Population Description: All randomized participants who received at least 1 dose of drug with Best Overall Response of Complete Response or Partial Response.5 participants were censored.

End point type	Secondary

End point timeframe:

First Observation of CR or PR until Progressive Disease or Death Due to Any Cause (Up to 23 Months)

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	55[2]			
Units: months				
median (confidence interval 90%)	8.7 (7 to 99999)			

Notes:

[2] - 99999 = Upper limit is not estimable based on sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum Plasma Concentration (Cmax) of LY2603618

End point title	Pharmacokinetics (PK): Maximum Plasma Concentration (Cmax) of LY2603618

End point description:

Analysis Population Description : All randomized participants who received at least 1 dose of drug and had evaluable PK data

End point type	Secondary

End point timeframe:

Day 2 and Day 3 of Cycle 1 and Cycle 2: Prior to End of Infusion (EOI); EOI + 1-2 hr; EOI + 4-6 hr; EOI + 20-28 hr; anytime on Day 8 of Cycle 1 and Cycle 2

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	48[3]			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 2/Cycle 1 (n=41)	3430 (± 50)			
Day 2/Cycle 2 (n=48)	3560 (± 40)			

Notes:

[3] - The geometric coefficient of variation is a percentage.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum Plasma Concentration (Cmax) of Pemetrexed

End point title	PK: Maximum Plasma Concentration (Cmax) of Pemetrexed

End point description:

Analysis Population Description : All randomized participants who received at least 1 dose of drug and evaluable PK data.

End point type	Secondary

End point timeframe:

Day 1 and Day 2 of Cycle 1 and Cycle 2: Prior to End of Infusion (EOI); EOI + 1-2 hour (hr); EOI + 4-6-hr; EOI + 20-28 hr

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	43[4]			
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Day 1/Cycle 1 (n=40)	102 (± 50)			
Day 1/Cycle 2 (n=43)	96.8 (± 42)			

Notes:

[4] - The geometric coefficient of variation is a percentage.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under the plasma concentration vs. time Curve from time zero to infinity [AUC(0-∞)] of Pemetrexed

End point title	PK: Area Under the plasma concentration vs. time Curve from time zero to infinity [AUC(0-∞)] of Pemetrexed

End point description:

Analysis Population Description : All randomized participants who received at least 1 dose of drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Day 1 and Day 2 of Cycle 1 and Cycle 2: Prior to End of Infusion (EOI); EOI + 1-2 hour (hr); EOI + 4-6-hr; EOI + 20-28 hr

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	43[5]			
Units: microgram*hour per milliliter (µg*hr/mL)				
geometric mean (geometric coefficient of variation)				
Day 1/Cycle 1(n=40)	193 (± 31)			
Day 1/Cycle 2(n=43)	202 (± 33)			

Notes:

[5] - The geometric coefficient of variation is a percentage.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under the plasma concentration vs. time Curve from time zero to infinity [AUC(0-∞)] of LY2603618

End point title	PK: Area Under the plasma concentration vs. time Curve from time zero to infinity [AUC(0-∞)] of LY2603618

End point description:

Analysis Population Description: All randomized participants who received at least 1 dose of drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Day 2 and Day 3 of Cycle 1 and Cycle 2: Prior to End of Infusion (EOI); EOI + 1-2 hr; EOI + 4-6 hr; EOI + 20-28 hr; anytime on Day 8 of Cycle 1 and Cycle 2

End point values	LY2603618 and Pemetrexed			
Subject group type	Reporting group			
Number of subjects analysed	48[6]			
Units: nanograms*hour per milliliter (ng*h/mL)				
geometric mean (geometric coefficient of variation)				
Day 2/Cycle 1(n=41)	38000 (± 85)			
Day 2/Cycle 2(n=48)	41500 (± 88)			

Notes:

[6] - The geometric coefficient of variation is a percentage.

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:

I2I-MC-JMMD

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	LY2603618-150mg/m2+PEMETREXED-500mg/m2

Reporting group description: -

Serious adverse events	LY2603618-150mg/m2+PEMETREXED-500mg/m2		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 55 (29.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
pericardial effusion malignant			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
road traffic accident			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
spinal compression fracture			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
tibia fracture				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
convulsion				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
asthenia				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
febrile neutropenia				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
neutropenia				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
thrombocytopenia				
alternative dictionary used: MedDRA 14.1				

subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
gastritis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
haemoptysis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pleural effusion			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
pneumothorax			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
pulmonary embolism				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
dermatitis				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
confusional state				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
pneumonia				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
pseudomembranous colitis				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
sepsis				
alternative dictionary used: MedDRA 14.1				

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LY2603618-150mg/m2+PEMETREXED-500mg/m2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 55 (94.55%)		
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	7		
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Vascular disorders			
flushing			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
headache			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	12		
leukopenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	13		
neutropenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	35		
thrombocytopenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
General disorders and administration site conditions			
face oedema			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
fatigue			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	20 / 55 (36.36%)		
occurrences (all)	27		
pyrexia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Gastrointestinal disorders			

abdominal pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
constipation			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	15		
diarrhoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	7		
dyspepsia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
nausea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	28		
stomatitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
vomiting			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	8		
dyspnoea			
alternative dictionary used:			

MedDRA 14.1 subjects affected / exposed occurrences (all) haemoptysis alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all) nasal congestion alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all)	7 / 55 (12.73%) 7 3 / 55 (5.45%) 3 3 / 55 (5.45%) 3		
Skin and subcutaneous tissue disorders rash alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4		
Musculoskeletal and connective tissue disorders back pain alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all) myalgia alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 6 3 / 55 (5.45%) 3		
Infections and infestations herpes zoster alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3		
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 14.1 subjects affected / exposed occurrences (all)	9 / 55 (16.36%) 9		

dehydration			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
hypokalaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
hyponatraemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		

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