Clinical trial results:
LUME-Lung 3: A Phase I/II study of continuous oral treatment with BIBF 1120 added to standard gemcitabine/cisplatin therapy in first-line NSCLC patients with squamous cell histology

Summary

EudraCT number	2010-019707-32
Trial protocol	GB NL PT DE ES
Global end of trial date	17 January 2017

Results information

Result version number	v1
This version publication date	27 December 2017
First version publication date	27 December 2017

Trial information

Trial identification

Sponsor protocol code	1199.82

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01346540
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

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	19 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2013
Global end of trial reached?	Yes
Global end of trial date	17 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the Phase I part of the trial was to confirm that a dose of up to 200 mg twice daily (bid) nintedanib (BIBF 1120), added to gemcitabine and cisplatin, was safe and tolerable in patients with stage IIIB/IV or recurrent non-small cell lung cancer (NSCLC) with squamous cell histology.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2011
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	Spain: 6
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	10
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I was open-label, 3+3 dose-confirmation part of the trial aimed to confirm safety of nintedanib to a maximum dose of 200 milligram twice daily given in combination with the standard regimen of gemcitabine and cisplatin. Phase II was to be double-blind, randomised, placebo-controlled part, but this part of the trial was not conducted.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist sites which ensured that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria was violated.

Period 1

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

Blinding implementation details:

Phase I was the open-label, 3+3 dose-confirmation part.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib 150 milligram

Arm description:

Patient received 150 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

150 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled.

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

Dosage and administration details:

Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle.

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

Dosage and administration details:

Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Arm title	Nintedanib 200 milligram

Arm description:

Patient received 200 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

200 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled.

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

Dosage and administration details:

Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

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

Dosage and administration details:

Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle.

Number of subjects in period 1[1]	Nintedanib 150 milligram	Nintedanib 200 milligram
Started	4	12
Completed	1	0
Not completed	3	12
Adverse event, serious fatal	-	2
Adverse event, non-fatal	-	2
Progressive disease-RECIST 1.1 criteria	3	8

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on the patients who were randomized after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib 150 milligram
Reporting group description:	
Patient received 150 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.	
Reporting group title	Nintedanib 200 milligram
Reporting group description:	
Patient received 200 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.	

Reporting group values	Nintedanib 150 milligram	Nintedanib 200 milligram	Total
Number of subjects	4	12	16
Age categorical			
All patients who received at least one dose of any study medication were included in the Treated Set (TS)			
Units: Subjects			

Age Continuous			
All patients who received at least one dose of any study medication were included in the Treated Set (TS)			
Units: years			
arithmetic mean	64.5	65.7	
standard deviation	± 10.9	± 5.0	-
Gender, Male/Female			
All patients who received at least one dose of any study medication were included in the Treated Set (TS)			
Units: Subjects			
Female	0	1	1
Male	4	11	15

End points

End points reporting groups

Reporting group title	Nintedanib 150 milligram

Reporting group description:

Patient received 150 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Reporting group title	Nintedanib 200 milligram

Reporting group description:

Patient received 200 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Primary: Number of participants with Dose Limiting Toxicities (DLTs) during first cycle for the determination of the Maximum Tolerated Dose (MTD)

End point title	Number of participants with Dose Limiting Toxicities (DLTs) during first cycle for the determination of the Maximum Tolerated Dose (MTD)[1]

End point description:

DLT: Non-hematological toxicity - Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 events excluding transient electrolyte abnormality, hyperuricemia and isolated elevation of gamma-glutamyl trans-peptidase. Gastrointestinal AEs (nausea, vomiting, diarrhoea, abdominal pain) or hypertension of CTCAE Grade ≥3 despite optimal supportive care/intervention. Alanine aminotransferase and or Aspartate aminotransferase elevation of CTCAE Grade ≥3. Haematological toxicity - Uncomplicated CTCAE Grade 4 neutropenia (that was not associated with fever of ≥38.5° Celsius) for >7 days (except during Cycle 1). CTCAE Grade 4 febrile neutropenia associated with fever ≥38.5º Celsius. A decrease in platelet levels to CTCAE Grade 4 or 3 associated with bleeding or requiring transfusion. The inability to resume nintedanib dosing within 14 days of stopping due to drug-related AE was also considered a DLT. All patients who received at least one dose of nintedanib were included in the Safety Set

End point type	Primary

End point timeframe:

Up to 21 days from first drug administration

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 endpoint was evaluated only descriptively. Thus, no statistical hypothesis test was tested.

End point values	Nintedanib 150 milligram	Nintedanib 200 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[2]	12[3]		
Units: Participants	0	0		

Notes:

[2] - Safety Set

[3] - Safety Set

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose (MTD) of nintedanib added to cisplatin/gemcitabine based on the occurrence of DLTs during treatment cycle 1.

End point title	Maximum Tolerated Dose (MTD) of nintedanib added to cisplatin/gemcitabine based on the occurrence of DLTs during treatment cycle 1.[4]

End point description:

The MTD was defined as the dose of nintedanib administered with gemcitabine/cisplatin at which no more than 1 of 6 patients experienced DLT (or one dose tier below that dose at which 2 or more of 6 patients experienced DLT) during the first 21-day treatment cycle. Any DLTs experienced after the start of the second treatment period were considered separately. All patients who received at least one dose of nintedanib were included in the Safety Set. 99999:MTD was not determined for this dose group.

End point type	Primary

End point timeframe:

Up to 21 days from first drug administration

Notes:

[4] - 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 endpoint was evaluated only descriptively. Thus, no statistical hypothesis test was tested.

End point values	Nintedanib 150 milligram	Nintedanib 200 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[5]	12[6]		
Units: Milligram	99999	200		

Notes:

[5] - Safety Set

[6] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.00

End point title	Incidence of adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.00

End point description:

Incidence of adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.00 with grade 1-5. For Phase I, all patients who received at least one dose of any study medication were included in the Treated Set.

End point type	Secondary

End point timeframe:

From the first drug administration until 28 days after last study drug administration, up to 804 days

End point values	Nintedanib 150 milligram	Nintedanib 200 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[7]	12[8]		
Units: Participants				
Grade 1	0	0		
Grade 2	0	0		
Grade 3	1	8		
Grade 4	3	2		
Grade 5	0	2		

Notes:

[7] - Treated Set

[8] - Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after last study drug administration, up to 804 days

Adverse event reporting additional description:

Adverse events ongoing from the end of the treatment visit were also captured.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Nintedanib 150 milligram

Reporting group description:

Patient received 150 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Reporting group title	Nintedanib 200 milligram

Reporting group description:

Patient received 200 milligram (mg) Nintedanib (BIBF 1120) soft gelatin capsules, administered orally twice daily until withdrawal criteria were fulfilled along with standard therapy of Gemcitabine and Cisplatin. Gemcitabine was administered as an intravenous infused dose of 1250 milligram per meter squared (mg/m2) on days 1 and 8 of each 21-day treatment cycle. Cisplatin was administered as an intravenous infused dose of 75 mg/m2 given on day 1 of each 21-day treatment cycle.

Serious adverse events	Nintedanib 150 milligram	Nintedanib 200 milligram	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	5 / 12 (41.67%)	
number of deaths (all causes)	1	7	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
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			

Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			

subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
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	Nintedanib 150 milligram	Nintedanib 200 milligram	
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 4 (100.00%)	12 / 12 (100.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	4 / 12 (33.33%)	
occurrences (all)	0	10	
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	6 / 12 (50.00%)	
occurrences (all)	1	13	
Chest discomfort			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	1	3	
Fatigue			

subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	
occurrences (all)	4	3	
Malaise			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	4	2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)	4 / 12 (33.33%)	
occurrences (all)	6	4	
Dry throat			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	3 / 4 (75.00%)	3 / 12 (25.00%)	
occurrences (all)	5	3	
Dyspnoea exertional			

subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	2 / 4 (50.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Haemoptysis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	4	2	
Hiccups			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Sputum increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 12 (33.33%)	
occurrences (all)	1	4	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	1	4	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	1	3	
Blood albumin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	3	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Blood sodium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Blood urea increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Blood uric acid increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	4	
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Monocyte count decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	4	
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	2 / 4 (50.00%)	4 / 12 (33.33%)	
occurrences (all)	2	4	
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	6	
Injury, poisoning and procedural complications			
Tooth fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 4 (50.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Dizziness postural			

subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 4 (50.00%)	1 / 12 (8.33%)	
occurrences (all)	4	2	
Lethargy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 12 (25.00%)	
occurrences (all)	2	5	
Neutropenia			
subjects affected / exposed	3 / 4 (75.00%)	4 / 12 (33.33%)	
occurrences (all)	3	7	
Thrombocytopenia			
subjects affected / exposed	3 / 4 (75.00%)	4 / 12 (33.33%)	
occurrences (all)	6	4	
Ear and labyrinth disorders			
Deafness			

subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Ear discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	
occurrences (all)	1	8	
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Abdominal tenderness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	8 / 12 (66.67%)	
occurrences (all)	3	16	
Diarrhoea			

subjects affected / exposed	4 / 4 (100.00%)	5 / 12 (41.67%)	
occurrences (all)	5	9	
Dyspepsia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Gingival pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	4 / 4 (100.00%)	9 / 12 (75.00%)	
occurrences (all)	11	18	
Retching			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Toothache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	8 / 12 (66.67%)	
occurrences (all)	14	28	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 12 (33.33%)	
occurrences (all)	1	4	

Dry skin			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	2 / 4 (50.00%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Rash			
subjects affected / exposed	2 / 4 (50.00%)	3 / 12 (25.00%)	
occurrences (all)	4	4	
Rash maculo-papular			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Lower urinary tract symptoms			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	1	3	
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			

subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Periarthritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Sjogren's syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Oral candidiasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 4 (100.00%)	4 / 12 (33.33%)	
occurrences (all)	6	5	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Increased appetite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2013	This amendment made several changes to the Phase II part of the study that are not relevant here. The changes to the Phase I part of the study are detailed below: Clarification was added that liver function tests were to be carefully monitored during the study to fulfill the reporting requirements for Drug induced liver injury. Clarification in the reporting requirements for serious adverse events related to worsening of underlying disease or other pre-existing conditions were made. Clarification that patient's tumour assessments should be performed consistently every 6 weeks for as long as the patient is in the study.

Notes:

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.

This trial was prematurely discontinued (Phase II was not conducted) following Sponsor's decision not to continue the trial in this indication.

Notes: