Clinical trial results:
A Phase I-II evaluation of the safety and efficacy of the oral HSP90 inhibitor Debio 0932 in combination with standard of care in first- and second-line therapy of patients with Stage IIIb or IV Non-small Cell Lung Cancer - the HALO study (HSP90 inhibition And Lung cancer Outcomes)

Summary

EudraCT number	2011-005533-39
Trial protocol	GB ES HU
Global end of trial date	11 November 2014

Results information

Result version number	v1 (current)
This version publication date	11 August 2016
First version publication date	11 August 2016

Trial information

Trial identification

Sponsor protocol code	Debio0932-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Debiopharm International, S.A.
Sponsor organisation address	Case postale 5911, Chemin Messidor 5-7, Lausanne, Switzerland, 1002
Public contact	Vice President Clinical Research & Development, Debiopharm International, S.A., 41 21 321 01 11, info-international@debiopharm.com
Scientific contact	Vice President Clinical Research & Development, Debiopharm International, S.A., 41 21 321 01 11, info-international@debiopharm.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	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?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part A :To determine the MTD of Debio 0932 in combination with cisplatin/pemetrexed and cisplatin/gemcitabine in treatment-naïve patients with Stage IIIb or IV NSCLC and with docetaxel in previously treated patients with Stage IIIb or IV NSCLC.
Part B : To compare the effect of adding Debio 0932 to combination chemotherapy with cisplatin/pemetrexed and cisplatin/gemcitabine on the rate of PFS at 6 months in first-line therapy of patients with Stage IIIb or IV NSCLC.
Part C : To compare the effect of adding Debio 0932 to docetaxel on the change in tumour size in second-line therapy of patients with Stage IIIb or IV NSCLC.

Protection of trial subjects:

An independent DMC was established prior to initiation of Part A. The main tasks of the DMC was to perform continuous cardiac safety monitoring (CCSM) and provide recommendations to the Sponsor concerning dose regimens and study continuation/discontinuation. Written approval of the study protocol and the informed consent was obtained from the appropriate independent ethics committees (IECs) prior to initiation of the study. These IECs were also notified of the end of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	France: 12
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	55
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

82 patients with Stage IIIb or IV non-small cell lung cancer were recruited to participate in this trial.

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

Are arms mutually exclusive?	Yes
Arm title	Regimen A - Debio 0932/Cisplatin/Pemetrexed

Arm description:

Debio 0932 administered in conjunction with standard chemotherapy care.

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

Dosage and administration details:

Pemetrexed 500 mg/m2 BSA was to be administered on Day 1 of each 21 day treatment cycle.

Investigational medicinal product name	Debio 0932
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Debio 0932 administered as daily oral tablets at a starting dose of 250 mg four times per day (QD).

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

Dosage and administration details:

Cisplatin 75 mg/m2 body surface area (BSA) administered on Day 1 of each 21-day treatment cycle.

Arm title	Regimen B: Debio 0932/Cisplatin/Gemcitabine

Arm description:

Debio 0932 administered in conjunction with standard chemotherapy care.

Arm type	Experimental
Investigational medicinal product name	Debio 0932
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: Debio 0932 administered as daily oral tablets at a starting dose of 250 mg four times per day (QD).	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use
Dosage and administration details: Gemcitabine 1250 mg/m2 BSA administered 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 drip use
Dosage and administration details: Cisplatin 75 mg/m2 body surface area (BSA) administered on Day 1 of each 21-day treatment cycle.	
Arm title	Regimen C: Debio 0932/Docetaxel
Arm description: Debio 0932 administered in conjunction with standard chemotherapy care.	
Arm type	Experimental
Investigational medicinal product name	Debio 0932
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Debio 0932 administered as daily oral tablets at a starting dose of 250 mg four times per day (QD).	
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use
Dosage and administration details: Docetaxel 60 or 75 mg/m2 BSA administered on Day 1 of each 21-day treatment cycle.	

Number of subjects in period 1	Regimen A - Debio 0932/Cisplatin/Pemetrexed	Regimen B: Debio 0932/Cisplatin/Gemcitabine	Regimen C: Debio 0932/Docetaxel
Started	28	19	35
Completed	0	0	0
Not completed	28	19	35
Lost to follow-up	28	19	35

Baseline characteristics

Reporting groups	
Reporting group title	Regimen A - Debio 0932/Cisplatin/Pemetrexed
Reporting group description:	
Debio 0932 administered in conjunction with standard chemotherapy care.	
Reporting group title	Regimen B: Debio 0932/Cisplatin/Gemcitabine
Reporting group description:	
Debio 0932 administered in conjunction with standard chemotherapy care.	
Reporting group title	Regimen C: Debio 0932/Docetaxel
Reporting group description:	
Debio 0932 administered in conjunction with standard chemotherapy care.	

Reporting group values	Regimen A - Debio 0932/Cisplatin/Pemetrexed	Regimen B: Debio 0932/Cisplatin/Gemcitabine	Regimen C: Debio 0932/Docetaxel
Number of subjects	28	19	35
Age categorical Units: Subjects			
Adults: 18-80 years	28	19	35
Age continuous Units: years			
arithmetic mean	60.29	60.89	57.03
standard deviation	± 9.22	± 8.67	± 10.77
Gender categorical Units: Subjects			
Female	9	3	11
Male	19	16	24

Reporting group values	Total		
Number of subjects	82		
Age categorical Units: Subjects			
Adults: 18-80 years	82		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	23		
Male	59		

End points

End points reporting groups

Reporting group title	Regimen A - Debio 0932/Cisplatin/Pemetrexed
Reporting group description:	
Debio 0932 administered in conjunction with standard chemotherapy care.	
Reporting group title	Regimen B: Debio 0932/Cisplatin/Gemcitabine
Reporting group description:	
Debio 0932 administered in conjunction with standard chemotherapy care.	
Reporting group title	Regimen C: Debio 0932/Docetaxel
Reporting group description:	
Debio 0932 administered in conjunction with standard chemotherapy care.	

Primary: Number of patients with dose limiting toxicities

End point title	Number of patients with dose limiting toxicities[1]
End point description:	

End point type	Primary
End point timeframe:	
6 weeks	

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: The limited amount of data for this terminated trial precluded analysis.

End point values	Regimen A - Debio 0932/Cisplatin/ Pemetrexed	Regimen B: Debio 0932/Cisplatin/ Gemcitabine	Regimen C: Debio 0932/Docetaxe l	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Patients				

Notes:

[2] - The limited amount of data for this terminated trial precluded analysis.

[3] - The limited amount of data for this terminated trial precluded analysis.

[4] - The limited amount of data for this terminated trial precluded analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 years and three months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Regimen A - Debio 0932/Cisplatin/Pemetrexed
Reporting group description: Debio 0932 administered in conjunction with standard chemotherapy care.	
Reporting group title	Regimen C: Debio 0932/Docetaxel
Reporting group description: Debio 0932 administered in conjunction with standard chemotherapy care.	
Reporting group title	Regimen B: Debio 0932/Cisplatin/Gemcitabine
Reporting group description: Debio 0932 administered in conjunction with standard chemotherapy care.	

Serious adverse events	Regimen A - Debio 0932/Cisplatin/Pemetrexed	Regimen C: Debio 0932/Docetaxel	Regimen B: Debio 0932/Cisplatin/Gemcitabine
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 28 (42.86%)	18 / 35 (51.43%)	9 / 19 (47.37%)
number of deaths (all causes)	5	5	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			

subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	12 / 28 (42.86%)	18 / 35 (51.43%)	9 / 19 (47.37%)
occurrences causally related to treatment / all	0 / 19	0 / 26	0 / 16
deaths causally related to treatment / all	0 / 2	0 / 5	0 / 3
Pulmonary oedema			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
Thrombocytopenia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutropenia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 35 (8.57%)	3 / 19 (15.79%)
occurrences causally related to treatment / all	0 / 0	2 / 5	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Ischaemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer			

subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diarrhoea			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue			

disorders			
Muscular weakness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	12 / 28 (42.86%)	18 / 35 (51.43%)	9 / 19 (47.37%)
occurrences causally related to treatment / all	0 / 19	0 / 28	0 / 16
deaths causally related to treatment / all	0 / 2	0 / 5	0 / 3
Bone pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia viral			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Lung abscess			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected dermal cyst			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Regimen A - Debio 0932/Cisplatin/Pemetrexed	Regimen C: Debio 0932/Docetaxel	Regimen B: Debio 0932/Cisplatin/Gemcitabine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)	35 / 35 (100.00%)	19 / 19 (100.00%)
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	2 / 19 (10.53%)
occurrences (all)	0	2	2
Thrombosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 28 (0.00%)	5 / 35 (14.29%)	0 / 19 (0.00%)
occurrences (all)	0	17	0
Asthenia			
subjects affected / exposed	22 / 28 (78.57%)	24 / 35 (68.57%)	18 / 19 (94.74%)
occurrences (all)	80	75	49
Influenza like illness			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	11 / 28 (39.29%)	8 / 35 (22.86%)	3 / 19 (15.79%)
occurrences (all)	16	10	5
Hypothermia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	7 / 28 (25.00%)	8 / 35 (22.86%)	10 / 19 (52.63%)
occurrences (all)	11	12	11
Pain			
subjects affected / exposed	2 / 28 (7.14%)	1 / 35 (2.86%)	2 / 19 (10.53%)
occurrences (all)	2	1	4
Oedema			

subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	2 / 28 (7.14%)	4 / 35 (11.43%)	0 / 19 (0.00%)
occurrences (all)	4	4	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 28 (28.57%)	7 / 35 (20.00%)	9 / 19 (47.37%)
occurrences (all)	9	9	11
Chest pain			
subjects affected / exposed	2 / 28 (7.14%)	1 / 35 (2.86%)	3 / 19 (15.79%)
occurrences (all)	2	1	3
Dyspnoea-2			
subjects affected / exposed	3 / 28 (10.71%)	12 / 35 (34.29%)	8 / 19 (42.11%)
occurrences (all)	3	23	10
Dyspnoea exertional			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Musculoskeletal chest pain			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Pneumothorax			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	3 / 19 (15.79%)
occurrences (all)	2	5	5
Pulmonary embolism			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	1	3	1
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	3 / 28 (10.71%)	1 / 35 (2.86%)	2 / 19 (10.53%)
occurrences (all)	3	3	2
Insomnia			
subjects affected / exposed	4 / 28 (14.29%)	4 / 35 (11.43%)	4 / 19 (21.05%)
occurrences (all)	4	4	5
Depression			
subjects affected / exposed	2 / 28 (7.14%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 28 (10.71%)	4 / 35 (11.43%)	2 / 19 (10.53%)
occurrences (all)	4	19	3
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 28 (7.14%)	4 / 35 (11.43%)	0 / 19 (0.00%)
occurrences (all)	3	16	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 28 (3.57%)	5 / 35 (14.29%)	1 / 19 (5.26%)
occurrences (all)	1	10	1
Blood creatinine increased			
subjects affected / exposed	7 / 28 (25.00%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	13	3	1
Blood bilirubin increased			
subjects affected / exposed	0 / 28 (0.00%)	4 / 35 (11.43%)	0 / 19 (0.00%)
occurrences (all)	0	10	0
C-reactive protein increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ejection fraction decreased			

subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	2	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 28 (10.71%)	5 / 35 (14.29%)	3 / 19 (15.79%)
occurrences (all)	3	9	4
Neutrophil count increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 28 (3.57%)	4 / 35 (11.43%)	1 / 19 (5.26%)
occurrences (all)	2	4	1
Injury, poisoning and procedural complications			
Neurotoxicity			
subjects affected / exposed	8 / 28 (28.57%)	7 / 35 (20.00%)	3 / 19 (15.79%)
occurrences (all)	16	10	3
Ototoxicity			
subjects affected / exposed	7 / 28 (25.00%)	0 / 35 (0.00%)	3 / 19 (15.79%)
occurrences (all)	13	0	4
Skin toxicity			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	0	14	4
Hypothermia-2			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 28 (14.29%)	4 / 35 (11.43%)	2 / 19 (10.53%)
occurrences (all)	4	4	4
Dysgeusia			
subjects affected / exposed	3 / 28 (10.71%)	2 / 35 (5.71%)	4 / 19 (21.05%)
occurrences (all)	3	2	7
Ataxia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	5 / 28 (17.86%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	6	2	1
Headache			
subjects affected / exposed	5 / 28 (17.86%)	2 / 35 (5.71%)	6 / 19 (31.58%)
occurrences (all)	5	2	7
Neuropathy peripheral			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	1 / 19 (5.26%)
occurrences (all)	1	3	1
Somnolence			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Visual acuity reduced			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Vision blurred			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	14 / 28 (50.00%)	19 / 35 (54.29%)	14 / 19 (73.68%)
occurrences (all)	46	30	25
Febrile neutropenia			

subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	2 / 19 (10.53%)
occurrences (all)	0	2	2
Neutropenia			
subjects affected / exposed	12 / 28 (42.86%)	23 / 35 (65.71%)	13 / 19 (68.42%)
occurrences (all)	27	69	41
Leukopenia			
subjects affected / exposed	0 / 28 (0.00%)	5 / 35 (14.29%)	4 / 19 (21.05%)
occurrences (all)	0	14	7
Lymphopenia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	8	3	0
Thrombocytopenia			
subjects affected / exposed	3 / 28 (10.71%)	3 / 35 (8.57%)	9 / 19 (47.37%)
occurrences (all)	3	9	30
Thrombocytosis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	4 / 28 (14.29%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences (all)	5	0	0
Vertigo			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	2	2	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences (all)	0	4	1
Conjunctivitis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Eye pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	4 / 28 (14.29%)	2 / 35 (5.71%)	3 / 19 (15.79%)
occurrences (all)	5	2	3
Diarrhoea			
subjects affected / exposed	18 / 28 (64.29%)	27 / 35 (77.14%)	7 / 19 (36.84%)
occurrences (all)	35	70	9
Constipation			
subjects affected / exposed	8 / 28 (28.57%)	5 / 35 (14.29%)	7 / 19 (36.84%)
occurrences (all)	15	10	12
Dyspepsia			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	4	2	0
Haematemesis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hiccups			
subjects affected / exposed	5 / 28 (17.86%)	1 / 35 (2.86%)	0 / 19 (0.00%)
occurrences (all)	8	1	0
Stomatitis			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	2	2	1
Nausea			
subjects affected / exposed	20 / 28 (71.43%)	13 / 35 (37.14%)	15 / 19 (78.95%)
occurrences (all)	69	22	42
Reflux gastritis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	13 / 28 (46.43%)	8 / 35 (22.86%)	8 / 19 (42.11%)
occurrences (all)	32	12	19
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	1	6	0
Alopecia			
subjects affected / exposed	0 / 28 (0.00%)	9 / 35 (25.71%)	0 / 19 (0.00%)
occurrences (all)	0	11	0
Dermatitis acneiform			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	1	2	2
Nail disorder			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Lividity			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	2 / 19 (10.53%)
occurrences (all)	1	7	7
Rash maculo-papular			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
Rash			
subjects affected / exposed	4 / 28 (14.29%)	4 / 35 (11.43%)	4 / 19 (21.05%)
occurrences (all)	4	7	4
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Nocturia			

subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Renal failure			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	1 / 19 (5.26%)
occurrences (all)	1	1	4
Proteinuria			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 28 (10.71%)	8 / 35 (22.86%)	0 / 19 (0.00%)
occurrences (all)	3	15	0
Back pain			
subjects affected / exposed	5 / 28 (17.86%)	2 / 35 (5.71%)	1 / 19 (5.26%)
occurrences (all)	5	2	2
Muscle spasms			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Bone pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	2	7	0
Musculoskeletal pain			
subjects affected / exposed	4 / 28 (14.29%)	3 / 35 (8.57%)	1 / 19 (5.26%)
occurrences (all)	6	3	1
Myalgia			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 19 (0.00%)
occurrences (all)	2	8	0
Pain in extremity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	2 / 19 (10.53%)
occurrences (all)	0	4	3
Neck pain			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Candida infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Gingivitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Device related infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Respiratory tract infection			
subjects affected / exposed	3 / 28 (10.71%)	5 / 35 (14.29%)	0 / 19 (0.00%)
occurrences (all)	5	5	0
Superinfection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 28 (57.14%)	13 / 35 (37.14%)	11 / 19 (57.89%)
occurrences (all)	34	28	26
Dehydration			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			

subjects affected / exposed	3 / 28 (10.71%)	2 / 35 (5.71%)	3 / 19 (15.79%)
occurrences (all)	12	2	4
Hypercholesterolaemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Hypomagnesaemia			
subjects affected / exposed	4 / 28 (14.29%)	4 / 35 (11.43%)	2 / 19 (10.53%)
occurrences (all)	6	4	2
Hyponatraemia			
subjects affected / exposed	3 / 28 (10.71%)	4 / 35 (11.43%)	2 / 19 (10.53%)
occurrences (all)	4	4	2
Oedema-2			
subjects affected / exposed	3 / 28 (10.71%)	2 / 35 (5.71%)	0 / 19 (0.00%)
occurrences (all)	3	2	0

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? Yes

Date	Interruption	Restart date
10 November 2014	Trial termination	-

Notes:

Limitations and caveats

None reported