Clinical trial results:
A Phase Ib/II study of docetaxel with or without buparlisib as second line therapy for patients with advanced or metastatic squamous non-small cell lung cancer

Summary

EudraCT number	2013-000833-11
Trial protocol	SE IT DE ES GB BE HU NO FR
Global end of trial date	04 August 2015

Results information

Result version number	v2 (current)
This version publication date	20 October 2016
First version publication date	21 August 2016
Version creation reason	• Correction of full data set update disposition tablw

Trial information

Trial identification

Sponsor protocol code	CBKM120D2205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01911325
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	04 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For phase Ib:
To determine the maximum-tolerated dose (MTD) / recommended Phase II dose (RP2D) of buparlisib when administered orally in combination with every-3-week administration of docetaxel to adult patients with Stage IIIb or Stage IV NSCLC of squamous histology previously treated with platinum-based chemotherapy

For phase II:
To estimate the treatment effect of every-three-week administration of docetaxel and daily buparlisib or placebo on PFS in patients previously treated with platinum-based chemotherapy for advanced or metastatic squamous NSCLC

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2013
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	Korea, Republic of: 2
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	27
EEA total number of subjects	23

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)	13
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study did not proceed to the phase ll part of the study as the phase ll part was not conducted. So the results are based only on the phase l part of the study.

Pre-assignment

Screening details:

After signing the study Informed Consent Form, the screening assessments were done within 21 days prior to starting the treatment. Eligible patients started treatment only if a treatment cohort was open and the Sponsor had authorized the entry of the respective patient. Treatment was organized into cycles of 21 days.

Period 1

Period 1 title	Overall Study (Phase lb only) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase Ib: Buparlisib 80 mg/d

Arm description:

Buparlisib (BKM120) oral once daily: 80 mg dose levels to be tested in the dose escalation part of the trial in combination with docetaxel every three week intravenous (i.v.) infusion: 75 mg/m2 as per label.

Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Buparlisib was supplied as 10 mg and 50 mg hard gelatin capsules for oral daily dosing.

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

Dosage and administration details:

Docetaxel is available in single dose vials (1-vial-Taxotere®) containing 20 mg (1 mL) and 80 mg (4 mL) docetaxel. Each mL contains 20 mg docetaxel and 1.04 g polysorbate 80 and was taken every-three-week docetaxel at 75 mg/m2.

Arm title	Phase lb: Buparlisib 100 mg/d

Arm description:

Buparlisib (BKM120) oral once daily: 100 mg dose levels to be tested in the dose escalation part of the trial in combination with docetaxel every three week intravenous (i.v.) infusion: 75 mg/m2 as per label.

Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Buparlisib was supplied as 10 mg and 50 mg hard gelatin capsules for oral daily dosing.

Number of subjects in period 1	Phase Ib: Buparlisib 80 mg/d	Phase Ib: Buparlisib 100 mg/d
Started	16	11
Completed	0	0
Not completed	16	11
Consent withdrawn by subject	4	1
Physician decision	3	1
Adverse event, non-fatal	2	2
Death	1	1
progressive disease	6	4
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Phase Ib: Buparlisib 80 mg/d
Reporting group description:	
Buparlisib (BKM120) oral once daily: 80 mg dose levels to be tested in the dose escalation part of the trial in combination with docetaxel every three week intravenous (i.v.) infusion: 75 mg/m2 as per label.	
Reporting group title	Phase Ib: Buparlisib 100 mg/d
Reporting group description:	
Buparlisib (BKM120) oral once daily: 100 mg dose levels to be tested in the dose escalation part of the trial in combination with docetaxel every three week intravenous (i.v.) infusion: 75 mg/m2 as per label.	

Reporting group values	Phase Ib: Buparlisib 80 mg/d	Phase Ib: Buparlisib 100 mg/d	Total
Number of subjects	16	11	27
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	63	65	
standard deviation	± 5.9	± 5.9	-
Gender categorical			
Units: Subjects			
Female	0	3	3
Male	16	8	24

End points

End points reporting groups

Reporting group title	Phase Ib: Buparlisib 80 mg/d

Reporting group description:

Buparlisib (BKM120) oral once daily: 80 mg dose levels to be tested in the dose escalation part of the trial in combination with docetaxel every three week intravenous (i.v.) infusion: 75 mg/m2 as per label.

Reporting group title	Phase Ib: Buparlisib 100 mg/d

Reporting group description:

Buparlisib (BKM120) oral once daily: 100 mg dose levels to be tested in the dose escalation part of the trial in combination with docetaxel every three week intravenous (i.v.) infusion: 75 mg/m2 as per label.

Subject analysis set title	Dose determining set (DDS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The dose determining set included all patients who either met the minimum exposure criteria and had sufficient safety evaluations, or had experienced a DLT during Cycle 1.

Primary: Maximum tolerated dose (MTD) of buparlisisb

End point title	Maximum tolerated dose (MTD) of buparlisisb[1]

End point description:

MTD was defined as the highest safe dose of BKM120 given in combination with docetaxel in the first treatment cycle (Day 1 to Day 21). This is the highest dose not expected to cause DLT in 35% or more of the treated participants in the first cycle of treatment during the escalation part of the study. The analysis was performed on the dose determining set (DDS) population.

End point type	Primary

End point timeframe:

Day 1 to Day 21

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: Only summary stats conducted

End point values	Dose determining set (DDS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: mg				
number (not applicable)	80			

Statistical analyses

No statistical analyses for this end point

Primary: Recommended phase 2 dose (RP2D) of BKM120

End point title	Recommended phase 2 dose (RP2D) of BKM120[2]

End point description:

The RP2D was selected based on the safety, pharmacokinetic and pharmacodynamics profiles of the combination. The analysis was performed on the DDS population.

End point type	Primary

End point timeframe:

Day 1 to Day 21

Notes:

[2] - 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: Only summary stats conducted

End point values	Dose determining set (DDS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: mg				
number (not applicable)	80			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with overall response rate (ORR)

End point title	Percentage of participants with overall response rate (ORR)

End point description:

The ORR was defined as the percentage of patients with a best overall response of complete response (CR) or partial response (PR). CR is the disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR is at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

22 months

End point values	Phase Ib: Buparlisib 80 mg/d	Phase lb: Buparlisib 100 mg/d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: percentage of participants				
number (confidence interval 95%)	6.3 (0.2 to 30.2)	18.2 (2.3 to 51.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival as per local investigator assessments at 3 months

End point title	Progression free survival as per local investigator assessments

	at 3 months

End point description:

PFS was defined as the time from start date of study treatment until objective tumor progression (based on investigator’s assessment) or death from any cause. PFS was described using Kaplan-Meier curves.

End point type	Secondary

End point timeframe:

3 months

End point values	Phase Ib: Buparlisib 80 mg/d	Phase lb: Buparlisib 100 mg/d		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: percentage of patients events free				
number (confidence interval 95%)	37.04 (11.5 to 63.38)	46.67 (11.45 to 76.49)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Buparlisib 80mg/d

Reporting group description:

Buparlisib 80mg/d

Reporting group title	Buparlisib 100mg/d

Reporting group description:

Buparlisib 100mg/d

Serious adverse events	Buparlisib 80mg/d	Buparlisib 100mg/d	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)	9 / 11 (81.82%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	0	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
LIMB INJURY			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
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			
ANAEMIA			

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (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			
ASTHENIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
TOXIC SKIN ERUPTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Buparlisib 80mg/d	Buparlisib 100mg/d	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	11 / 11 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR ASSOCIATED FEVER			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
PHLEBITIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPOTENSION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
FLUSHING			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
AXILLARY PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ASTHENIA			
subjects affected / exposed	9 / 16 (56.25%)	8 / 11 (72.73%)	
occurrences (all)	11	9	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 16 (6.25%)	3 / 11 (27.27%)	
occurrences (all)	1	3	

HYPERTHERMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
CHEST DISCOMFORT			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
FATIGUE			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
FACE OEDEMA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
CHILLS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
PYREXIA			
subjects affected / exposed	5 / 16 (31.25%)	1 / 11 (9.09%)	
occurrences (all)	9	1	
PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	7 / 16 (43.75%)	2 / 11 (18.18%)	
occurrences (all)	8	2	
DYSPHONIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
COUGH			
subjects affected / exposed	6 / 16 (37.50%)	3 / 11 (27.27%)	
occurrences (all)	7	3	
HAEMOPTYSIS			

subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
HYPOXIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PRODUCTIVE COUGH			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
RHINORRHOEA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
EPISTAXIS			
subjects affected / exposed	2 / 16 (12.50%)	2 / 11 (18.18%)	
occurrences (all)	2	2	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	5	
MOOD ALTERED			
subjects affected / exposed	2 / 16 (12.50%)	3 / 11 (27.27%)	
occurrences (all)	3	3	
INSOMNIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
DEPRESSION			
subjects affected / exposed	2 / 16 (12.50%)	4 / 11 (36.36%)	
occurrences (all)	2	6	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
WEIGHT DECREASED			

subjects affected / exposed	4 / 16 (25.00%)	2 / 11 (18.18%)	
occurrences (all)	4	2	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
INSULIN C-PEPTIDE INCREASED			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
RADIATION PNEUMONITIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
PERIORBITAL HAEMATOMA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
INCISIONAL HERNIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
PROCEDURAL PAIN			

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
CARDIAC FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
TACHYCARDIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
ATAXIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
AGEUSIA			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
TREMOR			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PERIPHERAL SENSORY NEUROPATHY			

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
DYSGEUSIA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	3	
MEMORY IMPAIRMENT			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 16 (18.75%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
EOSINOPHILIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
LEUKOPENIA			
subjects affected / exposed	6 / 16 (37.50%)	8 / 11 (72.73%)	
occurrences (all)	13	17	
LYMPHOPENIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
NEUTROPENIA			
subjects affected / exposed	11 / 16 (68.75%)	10 / 11 (90.91%)	
occurrences (all)	22	22	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
TINNITUS			

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HYPOACUSIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Eye disorders			
AMBLYOPIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
VISUAL ACUITY REDUCED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
CHEILITIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
APHTHOUS STOMATITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
ABDOMINAL PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
CONSTIPATION			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
GINGIVAL PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
GASTROOESOPHAGEAL REFLUX DISEASE			

subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
DIARRHOEA			
subjects affected / exposed	6 / 16 (37.50%)	6 / 11 (54.55%)	
occurrences (all)	8	9	
DYSPEPSIA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
DRY MOUTH			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
DYSPHAGIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NAUSEA			
subjects affected / exposed	4 / 16 (25.00%)	4 / 11 (36.36%)	
occurrences (all)	5	6	
STOMATITIS			
subjects affected / exposed	5 / 16 (31.25%)	1 / 11 (9.09%)	
occurrences (all)	7	3	
PERIODONTAL DISEASE			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
VOMITING			
subjects affected / exposed	4 / 16 (25.00%)	2 / 11 (18.18%)	
occurrences (all)	7	3	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	5 / 16 (31.25%)	4 / 11 (36.36%)	
occurrences (all)	5	4	
DERMATITIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PRURITUS			
subjects affected / exposed	0 / 16 (0.00%)	4 / 11 (36.36%)	
occurrences (all)	0	6	

ERYTHEMA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
HYPERHIDROSIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NAIL DISORDER			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	2	
ONYCHOLYSIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
PURPURA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
TOXIC SKIN ERUPTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
RASH			
subjects affected / exposed	2 / 16 (12.50%)	3 / 11 (27.27%)	
occurrences (all)	3	6	
URTICARIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
SKIN REACTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

SKIN ULCER			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 11 (18.18%)	
occurrences (all)	1	3	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
BACK PAIN			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NECK PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
MYALGIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 16 (6.25%)	3 / 11 (27.27%)	
occurrences (all)	1	3	
Infections and infestations			
INFLUENZA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

CLOSTRIDIAL INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
GINGIVITIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
CONJUNCTIVITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PNEUMONIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ORAL CANDIDIASIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
ORAL HERPES			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ORAL FUNGAL INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ORAL INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
HYPOKALAEMIA			

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPERLIPASAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HYPERGLYCAEMIA			
subjects affected / exposed	13 / 16 (81.25%)	6 / 11 (54.55%)	
occurrences (all)	17	8	
DECREASED APPETITE			
subjects affected / exposed	6 / 16 (37.50%)	4 / 11 (36.36%)	
occurrences (all)	9	6	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
TETANY			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	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? No

Limitations and caveats

None reported