Clinical trial results:
A dose-finding phase Ib study followed by a randomized, double-blind phase II study of carboplatin and paclitaxel with or without buparlisib in patients with previously untreated metastatic non-small cell lung cancer (NSCLC) of squamous histology

Summary

EudraCT number	2012-005541-21
Trial protocol	IT DE FR ES GB CZ BE HU
Global end of trial date	18 June 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CBKM120D2204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01820325
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	18 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the MTD/RP2D of buparlisib when administered orally in combination with every-3-week carboplatin and paclitaxel to adult patients with previously untreated Stage IIIb (with malignant pleural or pericardial effusion) or Stage IV NSCLC of squamous histology

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	09 September 2013
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	Italy: 1
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	6
EEA total number of subjects	3

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)	2
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of approximately 12 to 18 evaluable patients were to be enrolled in the Phase Ib part of the study. Cohorts of 3 to 6 evaluable patients were to be enrolled in the dose-escalation part and at least six patients treated at the expected MTD level.

Pre-assignment

Screening details:

Eight patients were screened and 6 received treatment.

Period 1

Period 1 title	Treatment and FollowUp Post Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	80mg buparlisib INT+200+6

Arm description:

Buparlisib 80mg, intermittent (5 days on/2 days off) and paclitaxel administered once every 3 weeks as a single 3-hour (+/- 15 minutes) infusion of 200 mg/m2 body surface area (BSA) and carboplatin administered once every 3 weeks at an AUC=6 (using the Calvert formula) on Day 1 of a 21 day cycle. This intermittent dosing schedule was implemented with Amendment 1.

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 provided as 10 mg and 50 mg hard gelatin capsules, packaged in bottles.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was commercially available in 5 mL, 16.7 mL, and 50 mL multidose vials. If available, generic paclitaxel was used.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was commercially available in 5 mL, 15 mL, 45 mL, and 60 mL aqueous solution multidose vials. If available, generic carboplatin was used.

Arm title	80mg buparlisib OD+200+6

Arm description:

Buparlisib 80mg daily and paclitaxel administered once every 3 weeks as a single 3-hour (+/- 15 minutes) infusion of 200 mg/m2 body surface area (BSA) and carboplatin administered once every 3

weeks at an AUC=6 (using the Calvert formula).

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 provided as 10 mg and 50 mg hard gelatin capsules, packaged in bottles.

Number of subjects in period 1	80mg buparlisib INT+200+6	80mg buparlisib OD+200+6
Started	1	5
Completed	0	0
Not completed	1	5
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	2
Adverse event, non-fatal	-	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	80mg buparlisib INT+200+6
Reporting group description:	
Buparlisib 80mg, intermittent (5 days on/2 days off) and paclitaxel administered once every 3 weeks as a single 3-hour (+/- 15 minutes) infusion of 200 mg/m2 body surface area (BSA) and carboplatin administered once every 3 weeks at an AUC=6 (using the Calvert formula) on Day 1 of a 21 day cycle. This intermittent dosing schedule was implemented with Amendment 1.	
Reporting group title	80mg buparlisib OD+200+6
Reporting group description:	
Buparlisib 80mg daily and paclitaxel administered once every 3 weeks as a single 3-hour (+/- 15 minutes) infusion of 200 mg/m2 body surface area (BSA) and carboplatin administered once every 3 weeks at an AUC=6 (using the Calvert formula).	

Reporting group values	80mg buparlisib INT+200+6	80mg buparlisib OD+200+6	Total
Number of subjects	1	5	6
Age categorical Units: Subjects			
Adults (18-64 years)	0	2	2
From 65-84 years	1	3	4
Gender categorical Units: Subjects			
Female	1	2	3
Male	0	3	3

End points

End points reporting groups

Reporting group title	80mg buparlisib INT+200+6

Reporting group description:

Buparlisib 80mg, intermittent (5 days on/2 days off) and paclitaxel administered once every 3 weeks as a single 3-hour (+/- 15 minutes) infusion of 200 mg/m2 body surface area (BSA) and carboplatin administered once every 3 weeks at an AUC=6 (using the Calvert formula) on Day 1 of a 21 day cycle. This intermittent dosing schedule was implemented with Amendment 1.

Reporting group title	80mg buparlisib OD+200+6

Reporting group description:

Buparlisib 80mg daily and paclitaxel administered once every 3 weeks as a single 3-hour (+/- 15 minutes) infusion of 200 mg/m2 body surface area (BSA) and carboplatin administered once every 3 weeks at an AUC=6 (using the Calvert formula).

Primary: Determination of Maximum Tolerated Dose and Phase II Dose

End point title	Determination of Maximum Tolerated Dose and Phase II Dose[1]

End point description:

Maximum Tolerated Dose (MTD) or Recommended Phase II Dose (RP2D) determination of the combination treatment was to be based upon the estimation of the probability of dose-limiting toxicity (DLT) in Cycle 1 for patients in the dose-determining set. The study was terminated early by the Sponsor, before analyzing the primary objective to determine the MTD and/or RP2D.

End point type	Primary

End point timeframe:

Up to 6 cycles (21 day)

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 study was terminated prior to determination of the primary objective of the MTD/RP2D.

End point values	80mg buparlisib INT+200+6	80mg buparlisib OD+200+6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[2]	5[3]		
Units: mg	0	0		

Notes:

[2] - Study was terminated and analysis not done.

[3] - Study was terminated and analysis was not done.

Statistical analyses

No statistical analyses for this end point

Primary: Dose limiting toxicities at the time of DETC01

End point title	Dose limiting toxicities at the time of DETC01[4]

End point description:

A patient with multiple occurrences of DLTs under one treatment is counted only once in the AE category for that treatment. A patient with multiple DLTs within a primary system organ classes in Dose limiting toxicities at the time of DETC01counted only once in the total row.

End point type	Primary

End point timeframe:

Up to 21 days after the first dose of study treatment.

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: No analysis done.

End point values	80mg buparlisib INT+200+6	80mg buparlisib OD+200+6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3[5]		
Units: Patients				
Total Primary system organ class	0	2		
Total Gastrointestinal disorders	0	1		
Stomatitis (Gastrointestinal)	0	1		
Total Investigations	0	1		
Neutrophil count decreased (Investigations)	0	1		

Notes:

[5] - Three patients experienced dose limiting toxicities.

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 are reported in this record from 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	17.0

Reporting groups

Reporting group title	BKM120 80 mg INT + PTX200 + CRB6
Reporting group description: BKM120 80 mg INT + PTX200 + CRB6	
Reporting group title	BKM120 80 mg OD + PTX200 + CRB6
Reporting group description: BKM120 80 mg OD + PTX200 + CRB6	

Serious adverse events	BKM120 80 mg INT + PTX200 + CRB6	BKM120 80 mg OD + PTX200 + CRB6	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	3 / 5 (60.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
STOMATITIS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
HAEMOPTYSIS			

subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	BKM120 80 mg INT + PTX200 + CRB6	BKM120 80 mg OD + PTX200 + CRB6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	5 / 5 (100.00%)	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	3	
CHILLS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
FATIGUE			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
PYREXIA			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
BALANOPOSTHITIS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
EPISTAXIS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
OROPHARYNGEAL PAIN			

subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RHINORRHOEA			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	3	
RESPIRATORY DISORDER			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
DEPRESSION			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
DISORIENTATION			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
INSOMNIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 1 (100.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	6	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 1 (100.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
WEIGHT DECREASED			

subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
PARAESTHESIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
TREMOR			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	3	
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
LEUKOPENIA			
subjects affected / exposed	1 / 1 (100.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
NEUTROPENIA			
subjects affected / exposed	1 / 1 (100.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Eye disorders			

BLINDNESS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
LACRIMATION INCREASED			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
VISION BLURRED			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
DIARRHOEA			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
DYSPEPSIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
NAUSEA			
subjects affected / exposed	1 / 1 (100.00%)	4 / 5 (80.00%)	
occurrences (all)	1	8	
STOMATITIS			
subjects affected / exposed	0 / 1 (0.00%)	3 / 5 (60.00%)	
occurrences (all)	0	3	
VOMITING			
subjects affected / exposed	1 / 1 (100.00%)	2 / 5 (40.00%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
ERYTHEMA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
PRURITUS			

subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RASH			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	4	
SKIN DISCOLOURATION			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
SKIN EXFOLIATION			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
BACK PAIN			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
MYALGIA			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	3	
Infections and infestations			
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
RHINITIS			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			

DECREASED APPETITE			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
HYPERCALCAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPONATRAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 1 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2014	Amendment 1. A longer term assessment of safety and antitumor activity for the evaluation of MTD/RP2D was proposed and an Interim Analysis was to be conducted when all patients had completed 18 weeks of followup or had discontinued earlier. An intermittent dosing schedule of buparlisib (days 1-5 out of 7 days) in combination with carboplatin and paclitaxel every three weeks was introduced. PFS rate at 18 weeks from the start of treatment was added as a secondary endpoint in the Phase Ib part of the study. PK sampling was introduced in the Phase Ib part of the study. The use of granulocyte colony-stimulating factor (G-CSF) support during Cycle 1 in Phase Ib as per ASCO guidelines (Smith 2006) and local standard of care was introduced and recommended. The assessment of the ECOG performance scale was modified from a summary of the shift from baseline result to worst post-baseline result to an assessment of time to definitive deterioration of the ECOG performance. The staging classification for inclusion criteria was aligned according to the latest version UICC/AJCC version 7. The safety management guidelines of some of the most common drug related adverse events like hepatic toxicity, hyperglycemia and skin toxicity (maculopapular/acneiform rash, pruritus) were updated to align with the guidelines implemented at buparlisib clinical program level and in the new IB edition. The timeframe required for buparlisib interruption was modified from 21 to 28 days to allow a longer interval for rash recovery. The amount of tumor tissue required at Baseline for the analyanalysis of PI3K-related biomarkers was reduced. The upper limit for AST/ALT in patients without liver metastasis was increased to allow 1.5xULN for study inclusion. The requirement of performing pelvic magnetresonance imaging/computed tomography scan was changed from mandatory to clinically indicated.

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 study was early terminated by Novartis because of a challenging safety profile and rapidly evolving investigational landscape in this indication. The decision to end the trial was made during the Phase 1b portion of the trial.

Notes: