Clinical trial results:
Phase Ib/II multicenter study of buparlisib plus carboplatin or lomustine in patients with recurrent glioblastoma multiforme (GBM)

Summary

EudraCT number	2013-003129-27
Trial protocol	DE ES BE
Global end of trial date	07 July 2016

Results information

Result version number	v1 (current)
This version publication date	12 July 2017
First version publication date	12 July 2017

Trial information

Trial identification

Sponsor protocol code	CBKM120E2102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01934361
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	07 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the maximum tolerate dose (MTD) and/or recommended phase II dose (RP2D) of buparlisib plus carboplatin/lomustine in patients with recurrent GBM who have progressed after standard of care (SoC) (radiotherapy (RT) with temozolomide (TMZ) in combination and adjuvant) regardless of PI3K pathway activation status.

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	28 February 2014
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: 3
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Australia: 6
Worldwide total number of subjects	35
EEA total number of subjects	17

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)	27
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Based on overall safety profile and preliminary anti-tumor activity observed, decision was taken that Phase II part of the trial was not to be conducted.

Pre-assignment

Screening details:

Approx. 15 - 22 patients were planned to be enrolled in the phase lb part of the study. A total of 35 patients were treated and analyzed. In the buparlisib plus carboplatin cohort 1 the starting dose for buparlisib was 80 mg . After the 1st dose escalation meeting the dose of buparlisib was escalated to starting dose of 100mg for cohorts 2 and 3.

Period 1

Period 1 title	Phase l Dose Escalation Part (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Buparlisib 80 mg + Carboplatin

Arm description:

The starting dose of buparlisib was at 80 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks.

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 administered orally on a continuous daily schedule. Buparlisib was manufactured as 10mg and 50mg hard gelatin capsules.

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

Dosage and administration details:

Carboplatin intravenous infusion was administered at a dose of AUC 5 in a 21 day cycle (every 3 weeks).

Arm title	Buparlisib 100 mg + Carboplatin

Arm description:

The starting dose of buparlisib was at 100 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks.

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 administered orally on a continuous daily schedule. Buparlisib was manufactured as 10mg and 50mg hard gelatin capsules.

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

Dosage and administration details:

Carboplatin intravenous infusion was administered at a dose of AUC 5 in a 21 day cycle (every 3 weeks).

Arm title	Buparlisib 60 mg + Lomustine

Arm description:

The starting dose of buparlisib was at 60 mg once daily in combination with lomustine at a fixed dose of 100 mg/m² every 6 weeks.

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 administered orally on a continuous daily schedule. Buparlisib was manufactured as 10mg and 50mg hard gelatin capsules.

Investigational medicinal product name	Lomustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lomustine was given at a fixed dose of 100 mg/m² every 6 weeks.

Number of subjects in period 1	Buparlisib 80 mg + Carboplatin	Buparlisib 100 mg + Carboplatin	Buparlisib 60 mg + Lomustine
Started	3	14	18
Completed	3	14	18

Baseline characteristics

Reporting groups	
Reporting group title	Buparlisib 80 mg + Carboplatin
Reporting group description:	
The starting dose of buparlisib was at 80 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks.	
Reporting group title	Buparlisib 100 mg + Carboplatin
Reporting group description:	
The starting dose of buparlisib was at 100 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks.	
Reporting group title	Buparlisib 60 mg + Lomustine
Reporting group description:	
The starting dose of buparlisib was at 60 mg once daily in combination with lomustine at a fixed dose of 100 mg/m² every 6 weeks.	

Reporting group values	Buparlisib 80 mg + Carboplatin	Buparlisib 100 mg + Carboplatin	Buparlisib 60 mg + Lomustine
Number of subjects	3	14	18
Age categorical Units: Subjects			
Adults (18-64 years)	3	11	13
From 65-84 years	0	3	5
Gender categorical Units: Subjects			
Female	0	4	5
Male	3	10	13

Reporting group values	Total		
Number of subjects	35		
Age categorical Units: Subjects			
Adults (18-64 years)	27		
From 65-84 years	8		
Gender categorical Units: Subjects			
Female	9		
Male	26		

End points

End points reporting groups

Reporting group title	Buparlisib 80 mg + Carboplatin
Reporting group description:	
The starting dose of buparlisib was at 80 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks.	

Reporting group title	Buparlisib 100 mg + Carboplatin
Reporting group description:	
The starting dose of buparlisib was at 100 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks.	

Reporting group title	Buparlisib 60 mg + Lomustine
Reporting group description:	
The starting dose of buparlisib was at 60 mg once daily in combination with lomustine at a fixed dose of 100 mg/m² every 6 weeks.	

Primary: Number of patients with any grade Dose Limiting Toxicities (DLTs) by Preferred Term

End point title	Number of patients with any grade Dose Limiting Toxicities (DLTs) by Preferred Term[1]
End point description:	
The maximum tolerated dose (MTD) was defined as the highest drug dosage that did not cause medically unacceptable DLTs in more than 35% of the treated patients during the first cycle of treatment. MTD is reported by the number of dose limiting toxicities by Preferred Term (PT). MTD was confirmed in the carboplatin arm as100 mg per day. Buparlisib in combination with lomustine arm did not satisfy the criteria for confirmation of MTD. Although 17 patients were treated in the dose-escalation phase for the Carboplatin arms, only 16 were included in the dose determining set (DDS). In the DDS (in the buparlisib 100 mg arm), 1 patient was not evaluable in Cycle 1, had no DLT in Cycle 1 and did not have the required minimum treatment exposure.	

End point type	Primary
End point timeframe:	
21 days for carboplatin arm and 42 for lomustine	

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 descriptive statistical analysis were done for this endpoint.

End point values	Buparlisib 80 mg + Carboplatin	Buparlisib 100 mg + Carboplatin	Buparlisib 60 mg + Lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	13	12	
Units: Number of subjects				
Neutrophil count decreased	0	1	0	
Platelet count decreased	0	0	1	
Anxiety disorder	0	1	0	
Suicidal ideation	0	1	0	
Depression	0	0	2	
Thrombocytopenia	0	0	1	
Fatigue	0	0	1	
Pneumonitis	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival as per Investigator review

End point title	Progression Free Survival as per Investigator review

End point description:

PFS was defined as time from date of treatment start to the date of the event, which was the first documented disease progression per local Investigator assessment (according to RANO criteria) or death due to any cause. The date of progression was the earliest time when any RANO progression event (i.e. radiological progression) or death was observed with no more than one prior missing assessment since the last adequate assessment. If the patient was alive and progression free at the time of LPLV, the date of censoring was the date of the last adequate tumor assessment. If the patient started a new anti-neoplastic therapy (including new chemotherapy regimen or radiotherapy), the date of censoring was the date of the last adequate tumor assessment before the initiation of the therapy estimates. 95% CI for median PFS for each arm was calculated using method of Brookmeyer and Crowley (1982). No comparative statistical analyses were done.

End point type	Secondary

End point timeframe:

From start of treatment until event date or last adequate tumor assessment date prior to initiation of new anti-neoplastic therapy

End point values	Buparlisib 80 mg + Carboplatin	Buparlisib 100 mg + Carboplatin	Buparlisib 60 mg + Lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	14	18	
Units: months				
median (confidence interval 95%)	1.1 (1.1 to 26.2)	1.4 (1.2 to 1.6)	1.3 (1.2 to 1.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) as per Investigator assessment

End point title	Overall Response Rate (ORR) as per Investigator assessment

End point description:

Overall response rate (ORR) defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR), which included sustained and non-sustained responders. Partial or Complete Responses reported prior to any additional anticancer therapy was considered for ORR computation irrespective of the number of missed assessments before response. Exact binomial 95% CI for each arm are provided.

End point type	Secondary

End point timeframe:

every 6 weeks from start of treatment until disease progression, withdrawal consent, lost to follow-up, start of another anti-neoplastic therapy, or death, whichever occurred first up to 28 months

End point values	Buparlisib 80 mg + Carboplatin	Buparlisib 100 mg + Carboplatin	Buparlisib 60 mg + Lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	14	18	
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (0.8 to 90.6)	0 (0 to 23.2)	0 (0 to 18.5)	

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 up to 30 days after last study treatment. All Adverse Events reported in this record are from date of First Patient First Treatment up to 30 days after last study treatment.

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	19.0

Reporting groups

Reporting group title	Buparlisib 80 mg@+@Carboplatin
Reporting group description:	
Buparlisib 80 mg@+@Carboplatin	
Reporting group title	Buparlisib 100 mg@+@Carboplatin
Reporting group description:	
Buparlisib 100 mg@+@Carboplatin	
Reporting group title	Buparlisib 60 mg@+@Lomustine
Reporting group description:	
Buparlisib 60 mg@+@Lomustine	

Serious adverse events	Buparlisib 80 mg@+@Carboplatin	Buparlisib 100 mg@+@Carboplatin	Buparlisib 60 mg@+@Lomustine
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	4 / 18 (22.22%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (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
Blood creatinine increased			

subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (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
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (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
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (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			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (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 physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Large intestine perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
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			
Aspiration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (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
Confusional state			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (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			
Acute kidney injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (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
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (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

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

Non-serious adverse events	Buparlisib 80 mg@+@Carboplatin	Buparlisib 100 mg@+@Carboplatin	Buparlisib 60 mg@+@Lomustine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	14 / 14 (100.00%)	18 / 18 (100.00%)
Vascular disorders			

Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	4 / 18 (22.22%)
occurrences (all)	1	6	4
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Orthostatic hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	3 / 18 (16.67%)
occurrences (all)	0	1	3
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	3 / 3 (100.00%)	5 / 14 (35.71%)	8 / 18 (44.44%)
occurrences (all)	3	5	9
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Influenza like illness			

subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hiccups			
subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Sneezing			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Abulia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Anhedonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	3 / 18 (16.67%)
occurrences (all)	1	3	3
Anxiety disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	4 / 18 (22.22%)
occurrences (all)	1	0	4
Depressed mood			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	4 / 18 (22.22%)
occurrences (all)	1	3	4
Insomnia			
subjects affected / exposed	2 / 3 (66.67%)	3 / 14 (21.43%)	4 / 18 (22.22%)
occurrences (all)	2	3	6

Irritability			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Suicidal ideation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	3 / 18 (16.67%)
occurrences (all)	2	0	8
Aspartate aminotransferase			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Electrocardiogram qt prolonged			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Insulin c-peptide increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	2 / 18 (11.11%)
occurrences (all)	5	4	2
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	8 / 18 (44.44%)
occurrences (all)	1	4	8
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	3 / 18 (16.67%)
occurrences (all)	1	3	3
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Gilbert's syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Sinus tachycardia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Aphasia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Cognitive disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Depressed level of consciousness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Facial paresis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gait apraxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 3 (66.67%)	7 / 14 (50.00%)	5 / 18 (27.78%)
occurrences (all)	2	7	5
Hemianopia homonymous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Hemiparesis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	3 / 18 (16.67%)
occurrences (all)	1	0	3
Nervous system disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Quadrantanopia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Seizure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	3 / 18 (16.67%)
occurrences (all)	0	2	3
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	6 / 18 (33.33%)
occurrences (all)	0	0	7
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	4 / 18 (22.22%)
occurrences (all)	0	5	8
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	6 / 14 (42.86%)	4 / 18 (22.22%)
occurrences (all)	0	10	6
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eye pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Scleritis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	3 / 18 (16.67%)
occurrences (all)	1	5	3
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	3 / 18 (16.67%)
occurrences (all)	0	5	4
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	3 / 18 (16.67%)
occurrences (all)	0	1	4
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	6 / 14 (42.86%)	8 / 18 (44.44%)
occurrences (all)	2	6	11
Proctalgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	2 / 18 (11.11%)
occurrences (all)	5	3	2
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	2 / 3 (66.67%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin fissures			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Urticaria			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Micturition urgency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Urinary incontinence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Myalgia			

subjects affected / exposed	1 / 3 (33.33%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	1	1	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	4 / 14 (28.57%)	2 / 18 (11.11%)
occurrences (all)	0	4	2
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	3 / 18 (16.67%)
occurrences (all)	2	4	4
Hyperphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	4 / 18 (22.22%)
occurrences (all)	0	2	4
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Increased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2015	The purpose of this protocol amendment was to: Provide additional guidance for the management of liver toxicities and add guidelines for management of Posterior Reversible Encephalopathy Syndrome (PRES); Update clinical experience with buparlisib to be aligned with the latest Investigator Brochure (Edition 7); Provide Clarifications to enable the difference in the following terms Discontinuation of Study Treatment, Lost to Follow-up, and Withdrawal of Consent; Add possibility for ongoing patients to continue in a roll-over protocol and clarify the definition of the end of 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.

As of 30-Sep-2015, 35 patients were enrolled in the Phase Ib part of the study. The Phase II part of the study was not conducted based on the decision of the interim analysis conducted on 14-May-2015.

Notes: