Clinical trial results:
A Two-Part Phase 1/2a, Open-Label, Dose-Escalation Study to Evaluate the Tolerability and Preliminary Antitumour Activity of OPB-111001 in Patients with Advanced Cancers that are Poorly Responsive to Standard Anticancer Treatment

Summary

EudraCT number	2013-001249-15
Trial protocol	GB
Global end of trial date	08 September 2015

Results information

Result version number	v1 (current)
This version publication date	30 September 2016
First version publication date	30 September 2016

Trial information

Trial identification

Sponsor protocol code	314-12-401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02042885
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Novel Products GmbH
Sponsor organisation address	Erika-Mann-Str. 21, Munich, Germany, 80636
Public contact	Barbara Eschenbach, Otsuka Novel Products GmbH, +49 89-2060205-81, beschenbach@Otsuka-onpg.com
Scientific contact	Norbert Hittel, Otsuka Novel Products GmbH, +49 89-2060205-40, nhittel@Otsuka-onpg.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2015
Global end of trial reached?	Yes
Global end of trial date	08 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the tolerability profile of OPB-111001 and to establish the maximum-tolerated dose (MTD), recommended phase 2 dose (RP2D), or both in patients with cancer of the prostate, ovary, cervix, endometrium, breast, or salivary gland.

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research participants, no trial procedures were performed on trial participants until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 8 participants at 2 trial sites in 1 country.

Pre-assignment

Screening details:

Participants had screening evaluations between Day -1 and -14 before entering the first 14-day treatment cycle.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	IPDE Cohort 2 (OPB-111001 5mg)

Arm description:

Participants in intra-patient dose escalation (IPDE) cohort 2 had received 5mg OPB-111001 orally per week.

Arm type	Experimental
Investigational medicinal product name	OPB-111001 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During each cycle, participants received orally 5mg OPB-111001 per week.

Arm title	DE Cohort 2 (OPB-111001 10mg)

Arm description:

Participants in dose escalation cohort 2 received 10mg OPB-111001 orally per week.

Arm type	Experimental
Investigational medicinal product name	OPB-111001 10mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During each cycle, participants received orally 10mg OPB-111001 per week.

Arm title	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)

Arm description:

Participants in IPDE cohort 1 and dose escalation Cohort 3 had received 25 mg OPB-111001 orally per week.

Arm type	Experimental

Investigational medicinal product name	OPB-111001 25mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During each cycle, participants had received orally 25mg OPB-111001 per week.

Number of subjects in period 1	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)
Started	2	3	3
Completed	0	0	0
Not completed	2	3	3
Terminated by Sponsor	-	1	-
Progressive Disease	2	2	1
Adverse Events	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	IPDE Cohort 2 (OPB-111001 5mg)
Reporting group description:	
Participants in intra-patient dose escalation (IPDE) cohort 2 had received 5mg OPB-111001 orally per week.	
Reporting group title	DE Cohort 2 (OPB-111001 10mg)
Reporting group description:	
Participants in dose escalation cohort 2 received 10mg OPB-111001 orally per week.	

Reporting group title	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)
Reporting group description:	
Participants in IPDE cohort 1 and dose escalation Cohort 3 had received 25 mg OPB-111001 orally per week.	

Reporting group values	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)
Number of subjects	2	3	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	2
From 65-84 years	2	3	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	66.5	75.333	50.333
standard deviation	± 0.7071	± 2.0817	± 20.2073
Gender categorical Units: Subjects			
Female	0	0	2
Male	2	3	1

Reporting group values	Total		
Number of subjects	8		
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)	2		
From 65-84 years	6		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	2		
Male	6		

End points

End points reporting groups

Reporting group title	IPDE Cohort 2 (OPB-111001 5mg)
Reporting group description:	
Participants in intra-patient dose escalation (IPDE) cohort 2 had received 5mg OPB-111001 orally per week.	

Reporting group title	DE Cohort 2 (OPB-111001 10mg)
Reporting group description:	
Participants in dose escalation cohort 2 received 10mg OPB-111001 orally per week.	

Reporting group title	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)
Reporting group description:	
Participants in IPDE cohort 1 and dose escalation Cohort 3 had received 25 mg OPB-111001 orally per week.	

Primary: Determination of MTD or RP2D and Tolerability of OPB-111001 as defined by incidence of Adverse Events (AEs), changes from baseline in vital signs, clinical laboratory and electrocardiography assessments.

End point title	Determination of MTD or RP2D and Tolerability of OPB-111001 as defined by incidence of Adverse Events (AEs), changes from baseline in vital signs, clinical laboratory and electrocardiography assessments.[1]

End point description:

The primary safety endpoint was to determine the MTD or RP2D in the phase 1 with all safety data collected and in the phase 2a to evaluate the confirmatory tolerability of the MTD/RP2D of OPB-111001. All dose-limiting toxicity (DLTs) was entered as AEs. To support the determination of the MTD and/or RP2D adverse events analyses were presented that include only AEs. Treatment-emergent AEs (TEAEs) were defined as AEs occurring or worsening after the start of the first study treatment and up to 30 days after the last study treatment including all treatment cycles. AEs that started before start of study treatment were also considered TEAEs if any of the following conditions applied: Relationship of AE was reported as possibly related, probably related or related; The AE was serious; The AE led to discontinuation, interruption or dose reduction of study treatment; 4. the outcome of the AE was 'Death'.

End point type	Primary

End point timeframe:

MTD/RP2D - dose escalation part: After 1 or 3 cycles of treatment, determination of the MDR or RP2D and the tolerability of OPB-111001: continuously.

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: No inferential statistical analysis was performed for this primary safety endpoint.

End point values	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	3	
Units: Number of participants				
number (not applicable)				
Any TEAE	2	3	3	
TEAE related to OPB-111001	1	3	3	
TEAE with an outcome of death	0	0	0	

Serious TEAE	1	0	2	
TEAE leading to discontinuation of study drug	0	0	2	
DLT	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of antitumor activity as defined by Response Evaluation Criteria in Solid Tumours (RECIST)

End point title	Assessment of antitumor activity as defined by Response Evaluation Criteria in Solid Tumours (RECIST)

End point description:

Assessment of antitumor activity as defined by RECIST, Version 1.1: complete response(CR), partial response (PR), stable disease (SD), objective response rate(ORR) (CR + PR). The objective tumor response was classified as CR, PR, SD, PD, Non-CR/Non-PD or NE according to RECIST 1.1 and was determined every 4 cycles.

End point type	Secondary

End point timeframe:

Repeatedly every 8th week until end of study (average of 3 months approximately).

End point values	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	3	1	
Units: Number of participants				
number (not applicable)				
Prostate (SD)	0	2	0	
Prostate (non-CR/non-PD)	1	1	0	
Cervical PD	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Prostate-specific antigen (PSA) response in patients with prostate cancer.

End point title	Prostate-specific antigen (PSA) response in patients with prostate cancer.[2]

End point description:

PSA response in patients with prostate cancer: relative change determined according to Prostate Cancer Working Group 2 (PCWG2). For participants with prostate cancer, PSA values were measured as a tumor marker.

End point type	Secondary

End point timeframe:

Repeatedly (Cycle 1 to 3 on Day 1, then every 4th week) until end of study (average of 3 months approximately).

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for reporting arm IPDE Cohort 1 and DE Cohort 3 (25 mg) was not available due to very small sample size.

End point values	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: ng/mL				
median (full range (min-max))				
Cycle 2 Day 1 (N= 1, 3)	7.4 (7.4 to 7.4)	19 (5.7 to 22.8)		
Cycle 3 Day 1 (N= 1, 3)	25.1 (25.1 to 25.1)	-0.5 (-2.7 to 24)		
Cycle 5 Day 1 (N= 1, 3)	42.1 (42.1 to 42.1)	14.9 (3.8 to 78)		
Cycle 7 Day 1 (N= 1, 3)	58.1 (58.1 to 58.1)	55 (15.1 to 181)		
Cycle 9 Day 1 (N= 0, 1)	0 (0 to 0)	237 (237 to 237)		
1-week Follow-up (N= 1, 3)	70.1 (70.1 to 70.1)	184 (90 to 281)		
End of Study (N= 1, 2)	77.1 (77.1 to 77.1)	213 (101 to 325)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)

End point description:

TTF was defined as the time from start of treatment with OPB-111001 to discontinuation of OPB-111001 for any reason, including disease progression, treatment toxicity, subject's withdrawal and death. All participants who withdrew from the study because of any reason were analyzed as non-censored. Only participants who were still on treatment before the trial were stopped and discontinued treatment because of the stop of the trial were analyzed as censored at the date of discontinuation.

End point type	Secondary

End point timeframe:

At end of study (after average of 3 months approximately).

End point values	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	3	
Units: Days				
median (full range (min-max))				
Prostate (N= 1, 3, 0)	106 (106 to 106)	99 (93 to 127)	0 (0 to 0)	
Cervical (N= 0, 0, 1)	0 (0 to 0)	0 (0 to 0)	40 (40 to 40)	
Total (N= 1, 3, 1)	106 (106 to 106)	99 (93 to 127)	40 (40 to 40)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were defined as AEs occurring or worsening after the start of the first study treatment and up to 30 days after the last treatment including all treatment cycles (an approximate duration of 8.6 weeks).

Adverse event reporting additional description:

The safety population consisted of all enrolled participants who had received the study medication at least once.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	IPDE Cohort 2 (OPB-111001 5mg)

Reporting group description:

Participants in IPDE cohort 2 had received 5mg OPB-111001 orally per week.

Reporting group title	DE Cohort 2 (OPB-111001 10mg)

Reporting group description:

Participants in dose escalation cohort 2 received 10mg OPB-111001 orally per week.

Reporting group title	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)

Reporting group description:

Participants in IPDE cohort 1 and dose escalation Cohort 3 had received 25 mg OPB-111001 orally per week.

Serious adverse events	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Troponin I increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	IPDE Cohort 2 (OPB-111001 5mg)	DE Cohort 2 (OPB-111001 10mg)	IPDE Cohort 1 and DE Cohort 3 (OPB-111001 25 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	2	2	1
Oedema peripheral			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Hiccups			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Pharyngeal oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Troponin I increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	3
Tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Atrial flutter			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Bradyarrhythmia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Palpitations			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	4	9
Leukopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	3 / 3 (100.00%)
occurrences (all)	1	1	4
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	3 / 3 (100.00%)
occurrences (all)	0	3	6
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	3 / 3 (100.00%)
occurrences (all)	1	0	9
Abdominal discomfort			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Melaena			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Swollen tongue			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 2 (50.00%)	3 / 3 (100.00%)	2 / 3 (66.67%)
occurrences (all)	1	7	3
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Periorbital infection			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Fluid overload			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 September 2015	During the escalation phase of Regimen A (1 dose per week) with which the study began, 2 DLTs occurred in the lowest dose level described in the protocol; therefore, the study was temporarily put on hold in Jan 2015. Based on Data Monitoring Committee recommendations and evaluation of data, the sponsor decided on 08 September 2015 to prematurely terminate the study. Data interpretation was limited by the very small sample size (enrollment 1/5 of planned sample size; not powered for formal statistical analysis) and the open-label observation.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

During the escalation phase of Regimen-A, 2 DLTs occurred in the lowest dose level therefore, the study was temporarily put on hold in January 2015. After further evaluation of data, the sponsor decided on 08 September 2015 not to restart the study.

Notes: