Clinical trial results:
A Randomized Multicenter Study of Ibrutinib in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed/Refractory Multiple Myeloma

Summary

EudraCT number	2015-002191-25
Trial protocol	ES CZ DE GR
Global end of trial date	13 June 2018

Results information

Result version number	v1 (current)
This version publication date	25 September 2019
First version publication date	25 September 2019

Trial information

Trial identification

Sponsor protocol code	PCYC-1138-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02548962
WHO universal trial number (UTN)	-
Other trial identifiers	IND No:: 102,688

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	995 East Arques Avenue, Sunnyvale, United States, 94085-4521
Public contact	Medical Monitor Thorsten Graef, Pharmacyclics LLC, +1 (408) 215-3127, tgraef@pcyc.com
Scientific contact	Medical Monitor Thorsten Graef, Pharmacyclics LLC, +1 (408) 215-3127, tgraef@pcyc.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	25 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2018
Global end of trial reached?	Yes
Global end of trial date	13 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1:
-To determine the maximum tolerate dose (MTD)/maximum administered dose (MAD) and the Phase 2b dose of the ibrutinib, pomalidomide and dexamethasone combination.
- To determine the safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory Multiple Myeloma (MM).
Phase 2b:
- To evaluate the effect of ibrutinib in combination with pomalidomide and dexamethasone compared to placebo in combination with pomalidomide and dexamethasone on progression-free survival (PFS), as assessed by independent review committee (IRC), in subjects with relapsed/refractory MM.
Note: After completing Phase 1, the Sponsor elected not to move forward with Phase 2b.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practices and applicable local regulatory requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2016
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	Czech Republic: 4
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Australia: 1
Worldwide total number of subjects	11
EEA total number of subjects	7

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)	5
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase 1 study designed as an open-label, international, multi center, dose-finding study of Ibr+Pom+Dex. The study was conducted at a total of 11 sites in Australia, Czech Republic, Greece and the US.

Pre-assignment

Screening details:

Eligible subjects were required to have had a diagnosis of relapsed/refractory MM; also they have had to receive at least 2 prior lines of therapy, including lenalidomide and either bortezomib or carfilzomib; and have had demonstrated disease progression on or within 60 days of the completion of the most recent treatment regimen.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Patients were allocated first to 560 mg and passing the DLT threshold to 840 mg ibrutinib

Arms

Are arms mutually exclusive?	Yes
Arm title	560 mg Ibr+Pom+Dex

Arm description:

Cohort 1 (Ibr 560 mg+Pom+Dex)

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

Dosage and administration details:

Ibrutinib was administered orally once daily at a dose of 560 mg (4 x 140 mg capsules) in Cohort 1. Pomalidomide 4 mg was administered orally daily on Days 1-21 of each 28-day (4 week) cycle. Dexamethasone was administered orally at a dose of 40 mg weekly (reduced to 20 mg in subjects > 75 years).

Arm title	840 mg Ibr+ Pom+Dex

Arm description:

Cohort 2
(Ibr 840 mg+Pom+Dex)

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

Dosage and administration details:

Ibrutinib was administered orally once daily at a dose of 840 mg (6 x 140 mg capsules) in Cohort 2. Pomalidomide 4 mg was administered orally daily on Days 1-21 of each 28-day (4 week) cycle. Dexamethasone was administered orally at a dose of 40 mg weekly (reduced to 20 mg in subjects > 75 years).

Number of subjects in period 1	560 mg Ibr+Pom+Dex	840 mg Ibr+ Pom+Dex
Started	8	3
Completed	7	3
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	560 mg Ibr+Pom+Dex
Reporting group description:	
Cohort 1 (Ibr 560 mg+Pom+Dex)	
Reporting group title	840 mg Ibr+ Pom+Dex
Reporting group description:	
Cohort 2 (Ibr 840 mg+Pom+Dex)	

Reporting group values	560 mg Ibr+Pom+Dex	840 mg Ibr+ Pom+Dex	Total
Number of subjects	8	3	11
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)	5	0	5
From 65-84 years	3	3	6
85 years and over	0	0	0
Age continuous Units: years			
median	63.5	72.7	
full range (min-max)	53 to 81	67 to 77	-
Gender categorical Units: Subjects			
Female	3	3	6
Male	5	0	5

End points

End points reporting groups

Reporting group title	560 mg Ibr+Pom+Dex
Reporting group description:	
Cohort 1 (Ibr 560 mg+Pom+Dex)	
Reporting group title	840 mg Ibr+ Pom+Dex
Reporting group description:	
Cohort 2 (Ibr 840 mg+Pom+Dex)	

Primary: Overall response rate

End point title	Overall response rate[1]

End point description:

The overall response rate, defined as the proportion of subjects achieving a best overall response of PR or better per investigator assessment per IMWG at or prior to initiation of subsequent anticancer therapy. Overall response rate was the primary efficacy endpoint, whereas safety was the primary endpoint of the study.

End point type	Primary

End point timeframe:

Up to 3 years

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: This was an open-label, single arm, dose-escalation study. There was no statistical comparison performed.

End point values	560 mg Ibr+Pom+Dex	840 mg Ibr+ Pom+Dex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	3		
Units: percent				
number (not applicable)	37.5	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response

End point title	Clinical Benefit Response

End point description:

The clinical benefit response, defined as the proportion of subjects achieving a best overall response of MR or better per investigator assessment per IMWG at or prior to initiation of subsequent anticancer therapy.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	560 mg Ibr+Pom+Dex	840 mg Ibr+ Pom+Dex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	3		
Units: percent				
number (not applicable)	50	66.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug up to 30 days after the last dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Ibr 560 mg+Pom 4 mg+ Dex 40 mg
Reporting group description: -	
Reporting group title	Ibr 840 mg+ Pom 4 mg + Dex 40 mg
Reporting group description: -	

Serious adverse events	Ibr 560 mg+Pom 4 mg+ Dex 40 mg	Ibr 840 mg+ Pom 4 mg + Dex 40 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	3 / 3 (100.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (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			
Subdural haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			

subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (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			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ibr 560 mg+Pom 4 mg+ Dex 40 mg	Ibr 840 mg+ Pom 4 mg + Dex 40 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	3 / 3 (100.00%)	
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 8 (62.50%)	2 / 3 (66.67%)	
occurrences (all)	5	2	
Oedema peripheral			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Injection site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Psychiatric disorders			

Agitation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood creatine increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Mitral valve prolapse			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			

subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 8 (75.00%)	2 / 3 (66.67%)	
occurrences (all)	6	2	
Thrombocytopenia			
subjects affected / exposed	4 / 8 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Neutropenia			
subjects affected / exposed	4 / 8 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Increased tendency to bruise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Spontaneous haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Cerumen impaction			

subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Tympanic membrane perforation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Eye oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 3 (66.67%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 3 (66.67%)	
occurrences (all)	2	2	
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Melaena			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Stomatitis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Purpura senile			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Skin fissures			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

Limb discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Oral herpes			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	2 / 8 (25.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Furuncle			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Influenza			

subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Oral fungal infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Osteomyelitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Streptococcal sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2015	Updated the Phase 1 study design and study treatment to reflect a 3+3+3 dose escalation design, with up to 2 dose levels to determine the MTD/MAD and the Phase 2b dose of Ibr+Pom+Dex. • Increased the frequency of efficacy assessments occurring during the Response Followup Phase to be at a minimum of 4 weeks ±3 days to be consistent with on-treatment efficacy assessments for analysis of the primary endpoint. • Updated the protocol to align with the internal protocol template update. • Updated Study Evaluations and aligned language with Schedule of Assessments.
13 February 2017	• Updated the exclusion criteria regarding treatment-free interval for recent prior monoclonal antibody use from < 6 weeks to < 14 days (exclusion criteria #3). • Updated the protocol to align with the internal protocol template update. • Updated the protocol to align with ibrutinib Investigator's Brochure Version 10

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported