Clinical trial results:
Phase I/II dose-escalation study of oral administration of the Pan-Histone Deacetylase (HDAC) Inhibitor S 78454 in Hodgkin's Disease, non-Hodgkin Lymphoma and Chronic Lymphocytic Leukaemia

Summary

EudraCT number	2009-013691-47
Trial protocol	FR GB BE HU
Global end of trial date	10 February 2017

Results information

Result version number	v1 (current)
This version publication date	29 June 2017
First version publication date	29 June 2017

Trial information

Trial identification

Sponsor protocol code	CL1-78454-001 / PCYC-1401-CA

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 East Arques Avenue, Sunnyvale, United States, 94087
Public contact	Thorsten Graef, MD, PhD, Pharmacyclics LLC, + 1 408 408-774-0330,
Scientific contact	Thorsten Graef, MD, PhD, Pharmacyclics LLC, + 1 408 408-774-0330,

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	10 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2017
Global end of trial reached?	Yes
Global end of trial date	10 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I part:-
- To assess the MTD and the dose-limiting toxicities (DLTs).-

Phase II part:
- To assess the objective response rate at the recommended dose defined in the phase I part.-
- To assess the safety and tolerability.

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 Good Clinical Practices and applicable regulatory requirements, with the exception of known instances of non-conformance (Appendix 14) which were not considered to have an impact on the overall conclusions of this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 February 2010
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	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 81
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 17
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	135
EEA total number of subjects	105

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)	67
From 65 to 84 years	67
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a Phase 1/2, multicenter, open-label, non-randomized, non-comparative dose-escalation and efficacy evaluation of abexinostat conducted at multiple sites in Canada, Europe, and Asia conducted in 2 parts, Phase 1 and Phase 2.

Pre-assignment

Screening details:

In Phase 1, eligible subjects were adult men or women
with any measurable or evaluable histologically confirmed HD and NHL, and with any evaluable CLL.treated/relapsed
In Phase 2, eligible subjects were adult men or women with any measurable hist. confirmed and previously treated NHL in relapse or refractory to conventional, standard therapy

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Phase 1

Arm description:

Phase 1 (Dose Escalation)Assess the safety and tolerability of the oral capsule form of abexinostat given orally bid
4 hours apart during a 3-week cycle in patients with HD, non-Hodgkin’s lymphoma (NHL), and chronic lymphocytic leukemia (CLL) in terms of the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs) for each dosing schedule tested.
Determine the optimal dosing schedule and the associated recommended Phase 2 dose of the oral capsule form of abexinostat given orally bid 4 hours apart during a 3-week cycle.Secondary Objectives:
Determine the pharmacokinetic (PK) profile of the oral capsule form of abexinostat, its main metabolites, and its dose exposure relationship.
Determine the pharmacodynamic (PD) profile of the oral capsule form of abexinostat

Arm type	Experimental
Investigational medicinal product name	Abexinostat
Investigational medicinal product code	S 78454
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

In Schedule 1, 6 subjects were enrolled in the 30 mg/m2 cohort, 12 subjects (3 initial subjects + 9 additional subjects for the confirmatory phase) in the 45 mg/m2 cohort, and 3 subjects in the 60 mg/m2 cohort (Section 7.2). In Schedule 2, 3 subjects were enrolled in the 45 mg/m2 cohort, and 3 subjects in the 60 mg/m2 cohort. In Schedule 3, 3 subjects were enrolled in the 45 mg/m2 cohort, and 5 subjects in the 60 mg/m2 cohort.

Arm title	Phase 2

Arm description:

All 100 subjects were to receive a fixed dose of 80 mg bid.The aim of Phase 2 was exploratory

Arm type	Experimental

Investigational medicinal product name	abexinostat
Investigational medicinal product code	S 78454
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects in Phase 2 were to receive abexinostat bid 4 hours apart during a 3-week cycle at the RD and optimal dosing schedule defined in Phase 1. De-escalation to a lower dose and switching to a different schedule were permitted in cases of toxicity.
Phase 2 subjects received abexinostat orally bid, 4 hours apart for 14 consecutive days during a 3-week cycle (Dosing Schedule 1) at a fixed dose of 80 mg bid

Arm title	Efficacy Set Phase 1

Arm description:

Subjects who received at least one dose of study medication and who had at least one baseline and one post-baseline assessment.

Arm type	Experimental
Investigational medicinal product name	Abexinostat
Investigational medicinal product code	S 78454
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

In Schedule 1, 6 subjects were enrolled in the 30 mg/sqm cohort, 12 subjects (3 initial subjects + 9 additional subjects for the confirmatory phase) in the 45 mg/sqm cohort, and 3 subjects in the 60 mg/sqm cohort (Section 7.2). In Schedule 2, 3 subjects were enrolled in the 45 mg/sqm cohort, and 3 subjects in the 60 mg/sqm cohort. In Schedule 3, 3 subjects were enrolled in the 45 mg/sqm cohort, and 5 subjects in the 60 mg/sqm cohort.

Arm title	Efficacy Set Phase 2

Arm description:

Subjects who received at least one dose of study medication and who had at least one baseline and one post-baseline assessment.

Arm type	Experimental
Investigational medicinal product name	abexinostat
Investigational medicinal product code	S 78454
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects in Phase 2 were to receive abexinostat bid 4 hours apart during a 3-week cycle at the RD and optimal dosing schedule defined in Phase 1. De-escalation to a lower dose and switching to a different schedule were permitted in cases of toxicity.
Phase 2 subjects received abexinostat orally bid, 4 hours apart for 14 consecutive days during a 3-week cycle (Dosing Schedule 1) at a fixed dose of 80 mg bid

Number of subjects in period 1	Phase 1	Phase 2	Efficacy Set Phase 1
Started	35	100	32
Completed	35	100	32

Number of subjects in period 1	Efficacy Set Phase 2
Started	87

Completed	87

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1
Reporting group description:	
Phase 1 (Dose Escalation)Assess the safety and tolerability of the oral capsule form of abexinostat given orally bid 4 hours apart during a 3-week cycle in patients with HD, non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) in terms of the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs) for each dosing schedule tested. Determine the optimal dosing schedule and the associated recommended Phase 2 dose of the oral capsule form of abexinostat given orally bid 4 hours apart during a 3-week cycle.Secondary Objectives: Determine the pharmacokinetic (PK) profile of the oral capsule form of abexinostat, its main metabolites, and its dose exposure relationship. Determine the pharmacodynamic (PD) profile of the oral capsule form of abexinostat	
Reporting group title	Phase 2
Reporting group description:	
All 100 subjects were to receive a fixed dose of 80 mg bid.The aim of Phase 2 was exploratory	
Reporting group title	Efficacy Set Phase 1
Reporting group description:	
Subjects who received at least one dose of study medication and who had at least one baseline and one post-baseline assessment.	
Reporting group title	Efficacy Set Phase 2
Reporting group description:	
Subjects who received at least one dose of study medication and who had at least one baseline and one post-baseline assessment.	

Reporting group values	Phase 1	Phase 2	Efficacy Set Phase 1
Number of subjects	35	100	32
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)	22	48	20
From 65-84 years	13	51	12
85 years and over	0	1	0
Age continuous Units: years			
median	61	66.5	61
full range (min-max)	21 to 83	32 to 85	21 to 83
Gender categorical Units: Subjects			
Female	13	45	13
Male	22	55	19

Reporting group values	Efficacy Set Phase 2	Total	

Number of subjects	87	135	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	41	70	
From 65-84 years	46	64	
85 years and over	0	1	
Age continuous Units: years			
median	66		
full range (min-max)	32 to 85	-	
Gender categorical Units: Subjects			
Female	38	58	
Male	49	77	

End points

End points reporting groups

Reporting group title	Phase 1

Reporting group description:

Phase 1 (Dose Escalation)Assess the safety and tolerability of the oral capsule form of abexinostat given orally bid
4 hours apart during a 3-week cycle in patients with HD, non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) in terms of the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs) for each dosing schedule tested.
Determine the optimal dosing schedule and the associated recommended Phase 2 dose of the oral capsule form of abexinostat given orally bid 4 hours apart during a 3-week cycle.Secondary Objectives:
Determine the pharmacokinetic (PK) profile of the oral capsule form of abexinostat, its main metabolites, and its dose exposure relationship.
Determine the pharmacodynamic (PD) profile of the oral capsule form of abexinostat

Reporting group title	Phase 2

Reporting group description:

All 100 subjects were to receive a fixed dose of 80 mg bid.The aim of Phase 2 was exploratory

Reporting group title	Efficacy Set Phase 1

Reporting group description:

Subjects who received at least one dose of study medication and who had at least one baseline and one post-baseline assessment.

Reporting group title	Efficacy Set Phase 2

Reporting group description:

Subjects who received at least one dose of study medication and who had at least one baseline and one post-baseline assessment.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1][2]

End point description:

End point type	Primary

End point timeframe:

From first dose in a subject until subject left the study.

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 a Phase 1/2, multicenter, open-label, non-randomized, non-comparative study evaluating subjects with several different types of B-cell malignancies. In this context a strict statistical analysis did not appear meaningful.
[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: The objective of the Part 1 of this study was to assess the safety of increasing doses of abexinostat in subjects with hematological malignancies. Therefore, no formal statistical analysis has been conducted for these 35 subjects.

End point values	Efficacy Set Phase 1	Efficacy Set Phase 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	87		
Units: percent				
number (confidence interval 95%)	34.4 (20 to 50)	27.6 (20 to 40)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the 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	18.0

Reporting groups

Reporting group title	Overall trial Phase 1 and Phase 2

Reporting group description: -

Serious adverse events	Overall trial Phase 1 and Phase 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 135 (68.89%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 5		
Tumour compression			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coma			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Syncope			

subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical cord compression				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Balance disorder				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Pyrexia				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombosis in device				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-cardiac chest pain				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

Anaphylactic shock			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug hypersensitivity			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chylothorax			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Productive cough			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			

Platelet aggregation decreased				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colonoscopy				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatine increased				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Muscle strain				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foreign body				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Atrial fibrillation				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	62 / 135 (45.93%)			
occurrences causally related to treatment / all	131 / 132			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	14 / 135 (10.37%)			
occurrences causally related to treatment / all	14 / 17			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	10 / 135 (7.41%)			
occurrences causally related to treatment / all	7 / 16			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	5 / 135 (3.70%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	1 / 1			
Febrile bone marrow aplasia				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
Pancytopenia				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Abdominal pain				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal mass				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Urinary tract obstruction				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteoarthritis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Spinal osteoarthritis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 1		
Lung infection			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Cellulitis			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			

subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				

subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis externa				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
bronchopneumonia				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis haemophilus				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial Phase 1 and Phase 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 135 (99.26%)		
Investigations			
Weight decreased			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	15		

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	9		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	78 / 135 (57.78%)		
occurrences (all)	394		
Anaemia			
subjects affected / exposed	41 / 135 (30.37%)		
occurrences (all)	83		
Neutropenia			
subjects affected / exposed	35 / 135 (25.93%)		
occurrences (all)	124		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	55 / 135 (40.74%)		
occurrences (all)	77		
Fatigue			
subjects affected / exposed	16 / 135 (11.85%)		
occurrences (all)	17		
Pyrexia			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	17		
Oedema peripheral			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	65 / 135 (48.15%)		
occurrences (all)	119		
Nausea			

subjects affected / exposed	48 / 135 (35.56%)		
occurrences (all)	56		
Vomiting			
subjects affected / exposed	28 / 135 (20.74%)		
occurrences (all)	35		
Constipation			
subjects affected / exposed	17 / 135 (12.59%)		
occurrences (all)	19		
Abdominal pain			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	13		
Abdominal pain upper			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	9		
Dry mouth			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Abdominal distension			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	17		
Dyspnoea			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	9		
Epistaxis			

subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	16		
Pruritus			
subjects affected / exposed	10 / 135 (7.41%)		
occurrences (all)	11		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	19 / 135 (14.07%)		
occurrences (all)	24		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	13		
Influenza			
subjects affected / exposed	10 / 135 (7.41%)		
occurrences (all)	11		
Rhinitis			
subjects affected / exposed	10 / 135 (7.41%)		
occurrences (all)	10		
Bronchitis			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	11		
Urinary tract infection			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	14		
Upper respiratory tract infection			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	14		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	41 / 135 (30.37%)		
occurrences (all)	45		
Hyperkalaemia			
subjects affected / exposed	13 / 135 (9.63%)		
occurrences (all)	15		
Hypokalaemia			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2009	Original Protocol
01 December 2009	Amendment 1
29 June 2010	Amendment 2
23 May 2011	Amendment 3
19 July 2011	Amendment 5
29 May 2012	Amendment 6
20 June 2012	Amendment 7
28 March 2013	Amendment 9
10 July 2014	Amendment 10
13 April 2015	Amendment 14
15 October 2015	Amendment 15

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported