Clinical trial results:
An open-label, multi-center, expanded treatment protocol of oral panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and relapsed and refractory multiple myeloma

Summary

EudraCT number	2014-003239-21
Trial protocol	AT NO DE SE
Global end of trial date	15 May 2017

Results information

Result version number	v1 (current)
This version publication date	09 April 2020
First version publication date	09 April 2020

Trial information

Trial identification

Sponsor protocol code	CLBH589D2001X

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02568943
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 Pharmaceuticals AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals 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	15 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To provide early treatment access in patients with panobinostat and to further evaluate safety of panobinostat when used in combination with BTZ/Dex in patients with relapsed or relapsed and refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.

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	24 February 2015
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	Norway: 4
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Jordan: 2
Worldwide total number of subjects	55
EEA total number of subjects	48

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)	21
From 65 to 84 years	33
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening/baseline assessments were performed within 28 days prior to the first dose of panobinostat (including hematology, blood chemistry, and pregnancy tests, physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and electrocardiogram (ECG)).

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

Arm title	PAN+BTZ+Dex

Arm description:

Panobinostat was the study drug, Bortezomib and dexamethasone were administered in combination with panobinostat and were the combination drugs.
Treatment Phase 1 (Week 1-24 starting Cycle 1 Day 1)
- PAN given orally three times a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 3, 5, 8, 10 and 12)
- BTZ given iv or sc twice a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 4, 8, and 11)
- Dex given orally twice a week over 2 days with BTZ (twice a week), Weeks 1&2 of each 3-week cycle (Days 1, 2, 4, 5, 8, 9, 11, and 12)

Treatment Phase 2 (Week 25-48 starting Cycle 9 Day 1)
- PAN given orally three times a week, Weeks 1, 2, of each 3-week cycle (Days 1, 3, 5, 8, 10, and 12)
- BTZ given iv or sc once a week, Weeks 1, 2 of each 3-week cycle (Days 1 and 8)
- Dex given orally once per week over 2 days with BTZ, Weeks 1, 2 of each 3-week cycle (Days 1, 2, 8, and 9)

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	PAN, LBH589
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Treatment Phase 1 (Week 1-24 starting Cycle 1 Day 1): Panobinostat (PAN) (20 mg) given orally three times a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 3, 5, 8, 10 and 12).
Treatment Phase 2 (24 weeks starting Cycle 9 Day 1): PAN (20 mg) given orally three times a week, Weeks 1, 2, of each 3-week cycle (Days 1, 3, 5, 8, 10, and 12).

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	BTZ
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Treatment Phase 1 (Week 1-24 starting Cycle 1 Day 1): Bortezomib (BTZ) (1.3 mg/m^2) given IV or subcutaneous use twice a week, Weeks 1 & 2 of each 3 week cycle (Days 1, 4, 8, and 11).
Treatment Phase 2 (24 weeks starting Cycle 9 Day 1): BTZ (1.3 mg/m^2) given once a week IV or subcutaneous use, Weeks 1, 2 of each 3 week cycle (Days 1 and 8).

BTZ could be administered iv or sc at the investigator’s discretion; however, the patient was to be

treated consistently throughout the study by one route (either iv or sc).

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	DEX
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment Phase 1 (Week 1-24 starting Cycle 1 Day 1): Dexamethasone (Dex) (20 mg) given orally over two days twice a week with BTZ (twice a week), weeks 1&2 of each 3-week cycle (Days 1, 2, 4, 5, 8, 9, 11, and 12).
Treatment Phase 2 (24 weeks starting Cycle 9 Day 1): Dex (20 mg) orally once per week over two days with BTZ, Weeks 1, 2 of each 3-week cycle (Days 1, 2, 8, and 9).

Number of subjects in period 1	PAN+BTZ+Dex
Started	55
Completed	0
Not completed	55
Consent withdrawn by subject	2
Physician decision	1
Disease progression	20
Adverse event, non-fatal	7
Death	3
Administrative problems	1
Treatment duration completed as per protocol	21

Baseline characteristics

Reporting groups

Reporting group title	PAN+BTZ+Dex

Reporting group description:

Panobinostat was the study drug, Bortezomib and dexamethasone were administered in combination with panobinostat and were the combination drugs.
Treatment Phase 1 (Week 1-24 starting Cycle 1 Day 1)
- PAN given orally three times a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 3, 5, 8, 10 and 12)
- BTZ given iv or sc twice a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 4, 8, and 11)
- Dex given orally twice a week over 2 days with BTZ (twice a week), Weeks 1&2 of each 3-week cycle (Days 1, 2, 4, 5, 8, 9, 11, and 12)

Treatment Phase 2 (Week 25-48 starting Cycle 9 Day 1)
- PAN given orally three times a week, Weeks 1, 2, of each 3-week cycle (Days 1, 3, 5, 8, 10, and 12)
- BTZ given iv or sc once a week, Weeks 1, 2 of each 3-week cycle (Days 1 and 8)
- Dex given orally once per week over 2 days with BTZ, Weeks 1, 2 of each 3-week cycle (Days 1, 2, 8, and 9)

Reporting group values	PAN+BTZ+Dex	Total	
Number of subjects	55	55	
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)	21	21	
From 65-84 years	33	33	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	66.1		
standard deviation	± 9.18	-	
Gender categorical Units: Subjects			
Female	25	25	
Male	30	30	

End points

End points reporting groups

Reporting group title	PAN+BTZ+Dex

Reporting group description:

Panobinostat was the study drug, Bortezomib and dexamethasone were administered in combination with panobinostat and were the combination drugs.
Treatment Phase 1 (Week 1-24 starting Cycle 1 Day 1)
- PAN given orally three times a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 3, 5, 8, 10 and 12)
- BTZ given iv or sc twice a week, Weeks 1 & 2 of each 3-week cycle (Days 1, 4, 8, and 11)
- Dex given orally twice a week over 2 days with BTZ (twice a week), Weeks 1&2 of each 3-week cycle (Days 1, 2, 4, 5, 8, 9, 11, and 12)

Treatment Phase 2 (Week 25-48 starting Cycle 9 Day 1)
- PAN given orally three times a week, Weeks 1, 2, of each 3-week cycle (Days 1, 3, 5, 8, 10, and 12)
- BTZ given iv or sc once a week, Weeks 1, 2 of each 3-week cycle (Days 1 and 8)
- Dex given orally once per week over 2 days with BTZ, Weeks 1, 2 of each 3-week cycle (Days 1, 2, 8, and 9)

Primary: Percentage of participants experiencing an Adverse Event (AE)

End point title	Percentage of participants experiencing an Adverse Event

End point description:

AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy, or require changes in the study drug.

End point type	Primary

End point timeframe:

up to 48 weeks

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 statistical analyses have been performed for this primary end point.

End point values	PAN+BTZ+Dex			
Subject group type	Reporting group			
Number of subjects analysed	55[2]			
Units: percentage of participants				
number (not applicable)				
Any AE	98.2			
Any treatment-related AE	90.9			
Any SAE	52.7			
Any treatment-related SAE	32.7			
Any grade 3/4 AE	83.6			
Any grade 3/4 AE- suspected to be related to study	81.8			
AEs leading to discontinuation of treatment	18.2			
AEs leading to dose adjustment or temporary dose i	80.0			
AEs requiring additional therapy	41.8			

AEs of special interest	92.7			
On-treatment death	5.5			

Notes:

[2] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate based on European Group for Blood and Marrow Transplantation (EBMT) criteria per investigator assessment

End point title	Overall response rate based on European Group for Blood and Marrow Transplantation (EBMT) criteria per investigator assessment

End point description:

Overall response rate (ORR) was defined as the proportion of patients with CR or nCR or PR. Point estimate and exact 95% two-sided confidence interval of ORR were calculated.

End point type	Secondary

End point timeframe:

up to 48 weeks

End point values	PAN+BTZ+Dex			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percent of participants (%)				
number (confidence interval 95%)				
Overall response rate (ORR)	29.1 (17.63 to 42.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival by Investigator assessment, based on EBMT criteria

End point title	Progression free survival by Investigator assessment, based on EBMT criteria

End point description:

PFS was defined as the time from first dose date of study treatment to the date of the first documented disease progression or relapse or death due to any cause. PFS was based on EBMT criteria per investigator assessment. Progression free survival time (PFS) was summarized by using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

up to 48 weeks

End point values	PAN+BTZ+Dex			
Subject group type	Reporting group			
Number of subjects analysed	55[3]			
Units: percentage of participants (%)				
number (not applicable)				
Progression	23.6			
Relapse from CR	0			
Death	0			

Notes:

[3] - The Full Analysis Set (FAS) comprised all patients to whom study treatment was assigned.

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS

End point title	Median PFS
End point description: Median progression-free survival.	
End point type	Secondary
End point timeframe: up to 48 months	

End point values	PAN+BTZ+Dex			
Subject group type	Reporting group			
Number of subjects analysed	55[4]			
Units: months				
number (confidence interval 95%)	12.6 (4.0 to 9999.99)			

Notes:

[4] - FAS comprised all patients to whom study treatment was assigned. 9999.99 = not estimable.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	PAN+BTZ+Dex

Reporting group description:

The Safety Set included all patients who received at least one dose of study medication.

Serious adverse events	PAN+BTZ+Dex		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 55 (52.73%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 55 (1.82%)		
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 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Asthenia				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Drug withdrawal syndrome				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Pneumonitis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device failure				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
C-reactive protein increased				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Quadriparesis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	3 / 55 (5.45%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	8 / 55 (14.55%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Urethral haemorrhage				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bone lesion				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis astroviral				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Herpes zoster			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 1		
Lung infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Metapneumovirus infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			

subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PAN+BTZ+Dex		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 55 (96.36%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
C-reactive protein increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Platelet count decreased			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	16		
Weight decreased			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
White blood cell count decreased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		

Paraesthesia subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3 4 / 55 (7.27%) 4 3 / 55 (5.45%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 15 / 55 (27.27%) 24 3 / 55 (5.45%) 5 10 / 55 (18.18%) 12 28 / 55 (50.91%) 58		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 6 / 55 (10.91%) 7 28 / 55 (50.91%) 36 9 / 55 (16.36%) 10 4 / 55 (7.27%) 4		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4		
Constipation subjects affected / exposed occurrences (all)	9 / 55 (16.36%) 11		
Diarrhoea subjects affected / exposed occurrences (all)	29 / 55 (52.73%) 56		
Dyspepsia subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3		
Nausea subjects affected / exposed occurrences (all)	9 / 55 (16.36%) 13		
Vomiting subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 5		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 7		
Epistaxis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 5		
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4		
Back pain subjects affected / exposed occurrences (all)	7 / 55 (12.73%) 7		

Bone pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	7		
Infections and infestations			
Infection			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Oral candidiasis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Skin infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	9		
Urinary tract infection			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	11		
Dehydration			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
Hyperglycaemia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Hypocalcaemia			

subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	8		

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? No

Limitations and caveats

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

The study was not terminated early, but in June 2016, the decision was made to stop enrollment due to a choice of the Sponsor not to continue further development. Patients who were in the study were followed until termination according to protocol.

Notes: