Clinical trial results:
Phase Ib dose finding study of abiraterone acetate plus BEZ235 or BKM120 in patients with castration-resistant prostate cancer

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2012-002250-23
Trial protocol	ES
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	CBEZ235D2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01634061
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Dose escalation part: To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of abiraterone acetate (AA) plus BEZ235 (twice a day) and AA plus BKM120 (once a day) in castration resistant prostate cancer (CRPC) patients with AA failure.

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	26 September 2012
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	Belgium: 7
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	43
EEA total number of subjects	33

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)	11
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 54 patients were screened for the study and 11 of them were screen failures out of which there were two missing screen failure patients for whom no data
was entered in the database.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BEZ235 200mg bid + AA 1000mg qd

Arm description:

BEZ235 200mg bid + Abiraterone Acetate (AA) 1000mg qd

Arm type	Experimental
Investigational medicinal product name	BEZ235
Investigational medicinal product code	BEZ235
Other name	dactosilib
Pharmaceutical forms	Dispersion, Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

BEZ235 was supplied at dose strengths of 50 mg, 100 mg, 200 mg, 300 mg and 400 mg solid dispersion sachets (SDS) for oral use twice a day for 28 days

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone acetate (AA) 1000mg tablet for oral use once a day for 28 days

Arm title	BKM120 60mg qd + AA 1000mg qd

Arm description:

BKM120 60mg qd + AA 1000mg qd

Arm type	Experimental
Investigational medicinal product name	BKM120
Investigational medicinal product code	BKM120
Other name	buparlisib
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

BKM120 was supplied at dose strengths of 10 mg and 50 mg hard gelatin capsules total of 60mg daily given orally for 28 days.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone acetate (AA) 1000mg tablet for oral use once a day for 28 days

Arm title	BKM120 100mg qd + AA 1000mg qd

Arm description:

BKM120 100mg qd + AA 1000mg qd

Arm type	Experimental
Investigational medicinal product name	BKM120
Investigational medicinal product code	BKM120
Other name	buparlisib
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

BKM120 was supplied at dose strengths of 10 mg and 50 mg hard gelatin capsules total of 100mg daily given orally for 28 days.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone acetate (AA) 1000mg tablet for oral use once a day for 28 days

Number of subjects in period 1	BEZ235 200mg bid + AA 1000mg qd	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd
Started	18	5	20
Completed	0	0	0
Not completed	18	5	20
subject/guardian decision	5	3	3
Adverse event, non-fatal	9	-	7
progressive disease	4	2	10

Baseline characteristics

Reporting groups	
Reporting group title	BEZ235 200mg bid + AA 1000mg qd
Reporting group description:	
BEZ235 200mg bid + Abiraterone Acetate (AA) 1000mg qd	
Reporting group title	BKM120 60mg qd + AA 1000mg qd
Reporting group description:	
BKM120 60mg qd + AA 1000mg qd	
Reporting group title	BKM120 100mg qd + AA 1000mg qd
Reporting group description:	
BKM120 100mg qd + AA 1000mg qd	

Reporting group values	BEZ235 200mg bid + AA 1000mg qd	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd
Number of subjects	18	5	20
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)	4	0	7
From 65-84 years	14	5	13
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	69.3	71.4	66.8
standard deviation	± 7.58	± 7.86	± 7.38
Gender categorical Units: Subjects			
Female	0	0	0
Male	18	5	20

Reporting group values	Total		
Number of subjects	43		
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)	11		

From 65-84 years	32		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	0		
Male	43		

End points

End points reporting groups

Reporting group title	BEZ235 200mg bid + AA 1000mg qd
Reporting group description: BEZ235 200mg bid + Abiraterone Acetate (AA) 1000mg qd	
Reporting group title	BKM120 60mg qd + AA 1000mg qd
Reporting group description: BKM120 60mg qd + AA 1000mg qd	
Reporting group title	BKM120 100mg qd + AA 1000mg qd
Reporting group description: BKM120 100mg qd + AA 1000mg qd	

Primary: Maximum Therapeutic Dose (MTD) of Abiraterone acetate (AA) plus BEZ235 (twice a day) and AA plus

End point title	Maximum Therapeutic Dose (MTD) of Abiraterone acetate (AA) plus BEZ235 (twice a day) and AA plus[1]

End point description:

The MTD was not reached for all three arms. The dose escalation was stopped after cohort 3 at 200 mg twice a day due to challenging safety and tolerability profile of BEZ235.
The dose escalation was stopped after cohort 4 at 100 mg once a day as the combination was considered not feasible due to substantially lower exposure of BKM120 in this combination compared to the single agent exposure. The Full Analysis Set (FAS) comprised of all patients who received at least one dose of study treatment. Patients were analyzed according to the starting dose (BEZ235 or BKM120) they received. For efficacy analyses, the FAS was used.

End point type	Primary

End point timeframe:

12 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 planned statistical analyses were done for this outcome measure.

End point values	BEZ235 200mg bid + AA 1000mg qd	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18[2]	5[3]	20[4]	
Units: mg				
number (not applicable)	999	999	999	

Notes:

[2] - MTD not determined

[3] - MTD was not determined

[4] - MTD was not determined

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Prostate-Specific Antigen (PSA) from baseline at 12 weeks, by dose level, BKM120

End point title	Change in Prostate-Specific Antigen (PSA) from baseline at 12

	weeks, by dose level, BKM120[5]

End point description:

PSA change is defined as the change from baseline to the lowest PSA value at any time from the start of treatment. The Full Analysis Set (FAS) comprised of all patients who received at least one dose of study treatment. Patients were analyzed according to the starting dose BKM120 they received. For efficacy analyses, the FAS was used.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[5] - 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: No planned statistical analyses were done for this outcome measure.

End point values	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: ng/mL				
arithmetic mean (standard deviation)	350.91 (± 227.548)	369.62 (± 462.931)		

Statistical analyses

No statistical analyses for this end point

Secondary: Soft tissue best overall response, by dose level, BKM120 combination arm

End point title	Soft tissue best overall response, by dose level, BKM120 combination arm[6]

End point description:

Overall response rate: Complete response (CR) + Partial response (PR)
The Full Analysis Set (FAS) comprised of all patients who received at least one dose of study treatment. Patients were analyzed according to the starting dose BKM120 they received. For efficacy analyses, the FAS was used.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[6] - 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: No planned statistical analyses were done for this outcome measure.

End point values	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: participants				
number (confidence interval 95%)	0 (0 to 52.2)	0 (0 to 16.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression based on Bone Lesion (Radiological), by dose level,

End point title	Progression based on Bone Lesion (Radiological), by dose

End point description:

Progressive evaluation in bone per Investigator assessment and derived assessments based on PCWG2 guidelines were listed. The derived assessment categories
were summarized ("progressive disease", "no progression", "unknown" and "not assessed"). The Full Analysis Set (FAS) comprised of all patients who received at least one dose of study treatment. Patients were analyzed according to the starting dose BKM120 they received. For efficacy analyses, the FAS was used.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[7] - 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: No planned statistical analyses were done for this outcome measure.

End point values	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: participants				
number (not applicable)				
Progressive Disease (PD)	1	0		
Not progressed	2	9		
Not Assessed	0	0		
Unknown (UNK)	2	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic PK parameters Area Under Curve (AUCtau) at Cycle 1 Day 22, BKM120 combination arm

End point title	Pharmacokinetic PK parameters Area Under Curve (AUCtau) at Cycle 1 Day 22, BKM120 combination arm[8]

End point description:

AUCtau,ss Drug exposure over a dosing period, i.e. 12 hours for a BID regimen, 24 hours for QD, regimen. The pharmacokinetics of BKM120 were analyzed on Cycle 1 Day 22, based on the full PK profiles collected during the dose escalation part using the PAS set. Pharmacokinetic analysis set (PAS) consisted of patients who receive at least one dose of BKM120/BEZ235 or AA and have at least one non-

missing and non-zero concentration measurement of BKM120/BEZ235 or AA.

End point type	Secondary

End point timeframe:

Day 22

Notes:

[8] - 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: No planned statistical analyses were done for this outcome measure.

End point values	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: (h*ng/mL)				
arithmetic mean (standard deviation)	6830 (± 1030)	15100 (± 3230)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic PK parameters Cmax at Cycle 1 Day 22, BKM120 combination arm

End point title	Pharmacokinetic PK parameters Cmax at Cycle 1 Day 22, BKM120 combination arm[9]

End point description:

Cmax,ss The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration at steady state (mass x volume-1) The pharmacokinetics of BKM120 were analyzed on Cycle 1 Day 22, based on the full PK profiles collected during the dose escalation part using the PAS set. Pharmacokinetic analysis set (PAS) consisted of patients who receive at least one dose of BKM120/BEZ235 or AA and have at least one non-missing and non-zero concentration measurement of BKM120/BEZ235 or AA.

End point type	Secondary

End point timeframe:

Day 22

Notes:

[9] - 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: No planned statistical analyses were done for this outcome measure.

End point values	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: ng/mL				
arithmetic mean (standard deviation)	599 (± 140)	1180 (± 423)		

Statistical analyses

No statistical analyses for this end point

Secondary: BKM120 PK parameters Tmax atCycle 1 Day 22, BKM120 combination arm

End point title	BKM120 PK parameters Tmax atCycle 1 Day 22, BKM120 combination arm[10]

End point description:

Tmax,ss The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration at steady state. The pharmacokinetics of BKM120 were analyzed on Cycle 1 Day 22, based on the full PK profiles collected during the dose escalation part using the PAS set. Pharmacokinetic analysis set (PAS) consisted of patients who receive at least one dose of BKM120/BEZ235 or AA and have at least one non-missing and non-zero concentration measurement of BKM120/BEZ235 or AA.

End point type	Secondary

End point timeframe:

Day 22

Notes:

[10] - 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: MTD was not determined. No planned statistical analyses were done for this outcome measure.

End point values	BKM120 60mg qd + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: hours				
median (full range (min-max))	2 (1.5 to 2.97)	2.51 (0 to 6.08)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	BEZ235 200mg bid + AA 1000mg qd
Reporting group description:	
BEZ235 200mg bid + AA 1000mg qd	
Reporting group title	BKM120 100mg qd + AA 1000mg qd
Reporting group description:	
BKM120 100mg qd + AA 1000mg qd	
Reporting group title	BKM120 60mg qd + AA 1000mg qd
Reporting group description:	
BKM120 60mg qd + AA 1000mg qd	

Serious adverse events	BEZ235 200mg bid + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd	BKM120 60mg qd + AA 1000mg qd
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)	7 / 20 (35.00%)	1 / 5 (20.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
METASTASES TO SPINE			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
VENOUS THROMBOSIS			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
HAEMORRHAGIC TRANSFORMATION STROKE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE MARROW FAILURE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
General disorders and administration site conditions			
ASTHENIA			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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

Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
PNEUMONITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL FAILURE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
RENAL IMPAIRMENT			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE PAIN			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
PATHOLOGICAL FRACTURE			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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
Infections and infestations			
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (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

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

Non-serious adverse events	BEZ235 200mg bid + AA 1000mg qd	BKM120 100mg qd + AA 1000mg qd	BKM120 60mg qd + AA 1000mg qd
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	19 / 20 (95.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
HYPERTENSION			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
ORTHOSTATIC HYPERTENSION			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
HYPOTENSION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 18 (16.67%)	7 / 20 (35.00%)	2 / 5 (40.00%)
occurrences (all)	4	9	2
CHILLS			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
FACE OEDEMA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
FATIGUE			
subjects affected / exposed	6 / 18 (33.33%)	7 / 20 (35.00%)	3 / 5 (60.00%)
occurrences (all)	7	8	4
FEELING COLD			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
HYPERTHERMIA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
MALAISE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
MUCOSAL DRYNESS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
NON-CARDIAC CHEST PAIN			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
PYREXIA			
subjects affected / exposed	3 / 18 (16.67%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	5	2	0
Reproductive system and breast disorders			
ERECTILE DYSFUNCTION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
PELVIC PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
TESTICULAR PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
DYSPNOEA			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
DYSPHONIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
EPISTAXIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
HICCUPS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
PHARYNGEAL ERYTHEMA			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
PHARYNGEAL ULCERATION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
PNEUMONITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
SINUS CONGESTION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
AGITATION			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
CONFUSIONAL STATE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
DEPRESSION			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
DEPRESSED MOOD			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
INSOMNIA			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	2 / 5 (40.00%)
occurrences (all)	2	1	2
IRRITABILITY			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
MOOD ALTERED			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
SLEEP DISORDER			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Investigations			
AMYLASE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
GLYCOSYLATED HAEMOGLOBIN INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
INSULIN C-PEPTIDE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
LIPASE INCREASED			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
WEIGHT DECREASED			
subjects affected / exposed	5 / 18 (27.78%)	5 / 20 (25.00%)	0 / 5 (0.00%)
occurrences (all)	6	5	0
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
FALL			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
INJURY			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
PALPITATIONS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	1 / 5 (20.00%)
occurrences (all)	2	4	1
DYSGEUSIA			
subjects affected / exposed	3 / 18 (16.67%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
DYSKINESIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
EXTRAPYRAMIDAL DISORDER			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
HEADACHE			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	1 / 5 (20.00%)
occurrences (all)	1	3	1

PARAESTHESIA			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
PRESYNCOPE			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
SOMNOLENCE			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
RESTLESS LEGS SYNDROME			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
TREMOR			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
VITH NERVE PARALYSIS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 18 (16.67%)	6 / 20 (30.00%)	0 / 5 (0.00%)
occurrences (all)	5	6	0
LYMPHOPENIA			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
THROMBOCYTOPENIA			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
TINNITUS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Eye disorders			

LACRIMATION INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
PHOTOPHOBIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
ABDOMINAL PAIN			
subjects affected / exposed	3 / 18 (16.67%)	4 / 20 (20.00%)	0 / 5 (0.00%)
occurrences (all)	5	4	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
CHRONIC GASTRITIS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
CONSTIPATION			
subjects affected / exposed	4 / 18 (22.22%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	4	2	0
DIARRHOEA			
subjects affected / exposed	14 / 18 (77.78%)	6 / 20 (30.00%)	1 / 5 (20.00%)
occurrences (all)	23	12	2
DRY MOUTH			
subjects affected / exposed	3 / 18 (16.67%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
DYSPEPSIA			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
FLATULENCE			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
HAEMATOCHEZIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
HAEMORRHOIDS			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
NAUSEA			
subjects affected / exposed	10 / 18 (55.56%)	11 / 20 (55.00%)	3 / 5 (60.00%)
occurrences (all)	17	16	4
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
RECTAL TENESMUS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
REGURGITATION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
STOMATITIS			
subjects affected / exposed	7 / 18 (38.89%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	8	0	0
TOOTHACHE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
VOMITING			
subjects affected / exposed	5 / 18 (27.78%)	6 / 20 (30.00%)	2 / 5 (40.00%)
occurrences (all)	6	7	3
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

BLISTER			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
DRY SKIN			
subjects affected / exposed	0 / 18 (0.00%)	3 / 20 (15.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
ERYTHEMA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
NIGHT SWEATS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
PRURITUS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
RASH			
subjects affected / exposed	1 / 18 (5.56%)	4 / 20 (20.00%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
RASH ERYTHEMATOUS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
RASH MACULO-PAPULAR			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
RASH PAPULAR			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
URTICARIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

SKIN DISORDER			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
NOCTURIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
URINARY INCONTINENCE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	2 / 5 (40.00%)
occurrences (all)	1	3	2
BACK PAIN			
subjects affected / exposed	2 / 18 (11.11%)	4 / 20 (20.00%)	1 / 5 (20.00%)
occurrences (all)	3	7	2
FLANK PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
BONE PAIN			
subjects affected / exposed	3 / 18 (16.67%)	3 / 20 (15.00%)	0 / 5 (0.00%)
occurrences (all)	4	3	0
INTERVERTEBRAL DISC COMPRESSION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
MUSCLE SPASMS			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
MUSCULOSKELETAL DISCOMFORT			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	2 / 5 (40.00%)
occurrences (all)	2	1	2
MYALGIA			
subjects affected / exposed	4 / 18 (22.22%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	4	1	0
MYOPATHY			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
NECK PAIN			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	1 / 5 (20.00%)
occurrences (all)	2	3	1
PAIN IN EXTREMITY			
subjects affected / exposed	4 / 18 (22.22%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	5	2	0
SPINAL PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
PAIN IN JAW			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
DEVICE RELATED INFECTION			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
CONJUNCTIVITIS			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0

CYSTITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
GASTROENTERITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
OSTEOMYELITIS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
RHINITIS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	5 / 18 (27.78%)	9 / 20 (45.00%)	1 / 5 (20.00%)
occurrences (all)	5	10	1
DEHYDRATION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
FLUID OVERLOAD			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
HYPERGLYCAEMIA			
subjects affected / exposed	4 / 18 (22.22%)	9 / 20 (45.00%)	2 / 5 (40.00%)
occurrences (all)	6	17	3
HYPERKALAEMIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
HYPOCALCAEMIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
HYPOKALAEMIA			
subjects affected / exposed	3 / 18 (16.67%)	4 / 20 (20.00%)	2 / 5 (40.00%)
occurrences (all)	3	5	2
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
IRON DEFICIENCY			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2013	Amendment 1: The main purpose of this amendment is to provide clarification and guidance to the investigators on the management of BKM120 and BEZ235 related toxicities. These include modifications to the management of psychiatric disorders, hyperglycemia, stomatitis, and rash. The changes also include the time of meals and dosing relative to pharmacokinetic sampling.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: