Clinical trial results:
A phase III randomized, double blind placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer which progressed on or after aromatase inhibitor treatment

Summary

EudraCT number	2011-005524-17
Trial protocol	GB BE DE AT NL IT HU FR GR CZ SK
Global end of trial date	19 April 2019

Results information

Result version number	v1
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	CBKM120F2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01610284
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The co-primary objective was:
To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for all patients in the Main Study Cohort (known PI3K pathway activation status).
and/or
To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for all patients (Full Population)
or
To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for PI3K pathway activated sub-population.

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	07 August 2012
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	Argentina: 18
Country: Number of subjects enrolled	Australia: 39
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 46
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 119
Country: Number of subjects enrolled	China: 47
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 96
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Hungary: 24

Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Japan: 103
Country: Number of subjects enrolled	Korea, Republic of: 55
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Singapore: 10
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Spain: 103
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	United States: 156
Worldwide total number of subjects	1147
EEA total number of subjects	458

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)	707
From 65 to 84 years	432
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 274 centers in 29 countries worldwide (Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Japan, Republic of Korea, The Netherlands, Peru, Poland, Russia, Singapore, Slovakia, South Africa, Spain, Switzerland, Taiwan, Thailand, UK and USA.).

Pre-assignment

Screening details:

Approximately 1200 patients were planned to be enrolled in the study. A total of 1147 patients were randomized and analyzed (576 in the buparlisib + fulvestrant and 571 in the placebo + fulvestrant arm). Not completed: in Randomization Phase=Randomized and not Treated; in Treatment Phase=Discontinued study treatment per Protocol.

Period 1

Period 1 title	Randomization Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BKM120 100mg + Fulvestrant

Arm description:

BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.

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

Dosage and administration details:

100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Arm title	Placebo + Fulvestrant

Arm description:

BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.

Arm type	Placebo
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details: 500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Matching placebo to BKM120 100 mg once daily starting Cycle 1 Day 1	

Number of subjects in period 1	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant
Started	576	571
Safety Set (SS)	573 [1]	570
Completed	574	569
Not completed	2	2
Adverse event, serious fatal	-	1
Physician decision	1	1
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Safety Set (SS) = At least 1 dose of study treatment and a 1 post baseline safety assessment

Period 2

Period 2 title	Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	BKM120 100mg + Fulvestrant
Arm description: BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 100 mg once daily starting Cycle 1 Day 1	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Arm title	Placebo + Fulvestrant

Arm description:

BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to BKM120 100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Number of subjects in period 2	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant
Started	574	569
BKM120 pharmacokinetic analysis set	93	0
Full Pharmacokinetic Analysis Set (FPAS)	35	0
Completed	0	0
Not completed	574	569
Adverse event, serious fatal	6	5
Physician decision	27	24
Consent withdrawn by subject	55	23
Study terminated by Sponsor	18	15
Adverse event, non-fatal	80	12
Non-compliance with Study Treatment	8	1
Lost to follow-up	1	-
Disease Progression	377	486
Protocol deviation	2	3

Period 3

Period 3 title	Post-Treatment Efficacy Follow-Up Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	BKM120 100mg + Fulvestrant

Arm description:

BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily starting Cycle 1 Day 1

Arm title	Placebo + Fulvestrant

Arm description:

BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to BKM120 100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Number of subjects in period 3	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant
Started	89	29
Completed	0	0
Not completed	89	29
Adverse event, serious fatal	4	4
Physician decision	10	3
Consent withdrawn by subject	11	1
Adverse event, non-fatal	2	-
Disease Progression	24	8
New therapy for study indication	38	13

Baseline characteristics

Reporting groups	
Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description: BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description: BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	

Reporting group values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant	Total
Number of subjects	576	571	1147
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	329	378	707
>=65 years	247	193	440
Age Continuous Units: Years			
arithmetic mean	62.2	60.6	
standard deviation	± 10.20	± 10.08	-
Sex: Female, Male Units: Participants			
Female	576	571	1147
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	132	153	285
Black	5	16	21
Caucasian	402	376	778
Other	18	7	25
Unknown	19	18	37
Missing	0	1	1
ECOG Performance Status Units: Subjects			
Grade 0 = No Restrictions	333	344	677
Grade 1 = Only Light Work	231	211	442
Grade 2 = Only Self Care	11	16	27
Grade 3 = Only Limited Self-Care	1	0	1

End points

End points reporting groups

Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	
Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	
Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	

Primary: Progression Free Survival (PFS) based on Local Investigator assessment - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point title	Progression Free Survival (PFS) based on Local Investigator assessment - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point description:

Progression Free Survival (PFS) is defined as the time from date of randomization to the date of first radiologically documented progression or death due to any cause. If a patient did not progress or die at the time of the analysis data cut-off or start of new antineoplastic therapy, PFS was censored at the date of the last adequate tumor assessment before the earliest of the cut-off date or the start date of additional anti-neoplastic therapy. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria RECIST v1.1, as 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline and/or unequivocal progression of the non-target lesions and/or appearance of a new lesion. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm.

End point type	Primary

End point timeframe:

Date of randomization to the date of first documented tumor progression or death from any cause, whichever occurs first, reported between day of first patient randomized up to approximately 4 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Months				
median (confidence interval 95%)				
FAS-Full population	6.9 (6.8 to 7.8)	5.0 (4.0 to 5.2)		
FAS-Main cohort	6.8 (5.0 to 7.0)	4.5 (3.3 to 5.0)		
FAS-PI3K pathway activated	6.8 (4.9 to 7.1)	4.0 (3.1 to 5.2)		
FAS-PI3K pathway non-activated	6.9 (4.6 to 7.2)	4.6 (3.3 to 5.1)		
FAS-PI3K pathway unknown	8.7 (7.0 to 12.4)	6.8 (5.0 to 8.4)		

Statistical analyses

Statistical analysis title	FAS-Full population
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.89

Statistical analysis title	FAS-Main cohort
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.94

Statistical analysis title	FAS-PI3K pathway activated
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.015
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.97

Statistical analysis title	FAS-PI3K pathway non-activated
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.03

Statistical analysis title	FAS-PI3K pathway unknown
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.94

Secondary: Overall Survival (OS) - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point title	Overall Survival (OS) - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point description:

Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died by the date of analysis cut-off, OS was censored at the date of last known date patient alive. Patients were followed up for the duration of the study and for an expected average of every 3 months after end of treatment.

End point type	Secondary

End point timeframe:

Every 3 months following end of treatment visit, assessed for approximately 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Months				
median (confidence interval 95%)				
FAS-Full population	33.2 (30.0 to 37.3)	30.4 (27.9 to 32.2)		
FAS-Main cohort	30.9 (25.1 to 35.4)	28.9 (25.9 to 31.1)		
FAS-PI3K pathway activated	33.6 (23.8 to 40.0)	27.5 (24.4 to 31.3)		
FAS-PI3K pathway non-activated	28.8 (23.0 to 33.2)	30.0 (26.0 to 33.4)		
FAS-PI3K pathway unknown	42.3 (36.5 to 999)	36.0 (31.0 to 43.5)		

Statistical analyses

Statistical analysis title	FAS-Full population
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.045
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.02

Statistical analysis title	FAS-Main cohort
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.144
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.09

Statistical analysis title	FAS-PI3K pathway activated
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.08

Statistical analysis title	FAS-PI3K pathway non-activated
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.24

Statistical analysis title	FAS-PI3K pathway unknown
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.06

Secondary: Overall Response Rate (ORR) - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point title	Overall Response Rate (ORR) - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point description:

Overall Response Rate (ORR) is defined as the percentage of participants with best overall response of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST 1.1. ORR was analyzed in the full population. Response Evaluation Criteria in Solid Tumors (RECIST v1.1) for target/non target lesions: Complete Response (CR), disappearance of all target/non target lesions (all lymph nodes assigned as non-target lesions must be non-pathological in size (< 10 mm short axis)); Partial response (PR), >=30% decrease in the sum of the longest diameter of target lesions ; Overall Response (OR)= CR+PR. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of the first documented disease progression or date of death from any cause whichever came first, assessed for approximately 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Percentage of Participants				
number (confidence interval 95%)				
FAS-Full population	11.8 (9.3 to 14.7)	7.7 (5.7 to 10.2)		
FAS-Main cohort	11.0 (8.2 to 14.4)	7.8 (5.4 to 10.8)		

FAS-PI3K pathway activated	10.6 (6.6 to 16.0)	8.2 (4.6 to 13.1)		
FAS-PI3K pathway non-activated	11.3 (7.6 to 16.0)	7.5 (4.5 to 11.6)		
FAS-PI3K pathway unknown	14.1 (8.9 to 20.7)	7.5 (3.8 to 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point title	Clinical Benefit Rate (CBR) - Full Analysis Set (FAS) in Full population, Main Study Cohort and PI3K unknown cohort

End point description:

Clinical Benefit Rate (CBR) is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) or Non-CR/non-PD lasting more than 24 weeks based on local investigator's assessment according to RECIST 1.1. CBR was analyzed in the full population. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of the first documented disease progression or date of death from any cause whichever came first, assessed for approximately 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Percentage of Participants				
number (confidence interval 95%)				
FAS-Full population	43.8 (39.7 to 47.9)	42.0 (37.9 to 46.2)		
FAS-Main cohort	41.7 (37.0 to 46.5)	39.6 (34.9 to 44.5)		
FAS-PI3K pathway activated	40.4 (33.3 to 47.8)	40.8 (33.6 to 48.2)		
FAS-PI3K pathway non-activated	42.7 (36.3 to 49.2)	38.8 (32.6 to 45.2)		
FAS-PI3K pathway unknown	49.7 (41.4 to 58.0)	49.0 (40.7 to 57.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with On-Treatments Adverse Events, Serious Adverse Events and Deaths

End point title	Number of Participants with On-Treatments Adverse Events, Serious Adverse Events and Deaths

End point description:

Analysis of frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From first dose of study treatment to 30 days after last dose of study treatment, assessed for approximately 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	573	570		
Units: Percentage of Participants				
number (not applicable)				
On-treatment Adverse Event (AEs)	99.3	93.3		
On-treatment Serious Adverse Event (SAEs)	25.5	17.7		
On-treatment Deaths	2.1	2.3		
Primary cause of Death = Study Indication	1.0	1.2		
Primary cause of Death = Unknown reason	0.3	0		
Primary cause of Death = Disease Progression	0.3	0.4		
Primary cause of Death = Pneumonia	0.2	0		
Primary cause of Death = Septic Shock	0.2	0		
Primary cause of Death = Cerebral Haemorrhage	0	0.2		
Primary cause of Death = Cerebral Accident	0	0.2		
Primary cause of Death = Sudden Death	0	0.2		
Primary cause of Death = Urosepsis	0	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration-time profiles of BKM120 in combination with Fulvestrant at Cycle 2 Day 1

End point title	Plasma concentration-time profiles of BKM120 in combination with Fulvestrant at Cycle 2 Day 1[1]

End point description:

Plasma samples were collected from the first 200 BKM120-treated patients on Cycle 2 Day 1 (at pre-dose, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h and 24h [before Cycle 2 Day 2 dose] post-dose). Each cycle is 28 days. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Cycle2 Day1 (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours post-dose). Each cycle is 28 days.

Notes:

[1] - 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: BKM120 PK sampling only performed in BKM120 100mg + Fulvestrant treatment arm

End point values	BKM120 100mg + Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
C2D1 0hr (predose)	768.306 (± 69.1)			
C2D1 0.5hr	750.767 (± 55.4)			
C2D1 1hr	988.341 (± 49.2)			
C2D1 1.5hr	1082.086 (± 45.0)			
C2D1 2hr	1099.517 (± 36.4)			
C2D1 3hr	1081.123 (± 43.2)			
C2D1 4hr	935.485 (± 43.0)			
C2D1 6hr	795.555 (± 45.1)			
C2D1 8hr	808.886 (± 50.5)			
C2D1 24hr	712.336 (± 52.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Predose trough concentration-time profile of BKM120 in combination with Fulvestrant over time - Pharmacokinetic Analysis Set (PAS)

End point title	Predose trough concentration-time profile of BKM120 in combination with Fulvestrant over time - Pharmacokinetic Analysis Set (PAS)[2]

End point description:

Pre-dose samples were collected for trough concentrations at Cycle 2 Day 1, Cycle 2 Day 15 and Cycle 3 Day 1. Each cycle is 28 days. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1. Each cycle is 28 days.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: BKM120 PK sampling only performed in BKM120 100mg + Fulvestrant treatment arm

End point values	BKM120 100mg + Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	733.278 (± 75.6)			
Cycle 2 Day 15	735.172 (± 51.2)			
Cycle 3 Day 1	716.414 (± 84.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to definitive deterioration of the ECOG performance status - Full Analysis Set (FAS)

End point title	Median time to definitive deterioration of the ECOG performance status - Full Analysis Set (FAS)

End point description:

Time to definitive deterioration of the ECOG PS was defined as the time between the date of randomization and the date of the assessment at which definitive deterioration was seen. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Up to approx 27 months

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Months				
median (confidence interval 95%)	24.0 (17.1 to 999)	26.4 (19.9 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the global health status/Quality of life per EORTC-QLQ-C30

End point title	Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the global health status/Quality of life per

	EORTC-QLQ-C30

End point description:

The global health status/QoL scale score of the QLQ-C30 is identified as the primary PRO variable of interest. Physical Functioning (PF), Emotional Functioning (EF) and Social Functioning (SF) scale scores of the QLQ-C30. The time to definitive 10% deterioration is defined as the time from the randomization date to the date of an event, which is defined as a worsening (decrease) in score by at least 10% compared to baseline, with no later increase above this threshold observed during the course of the study or death due to any cause. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for a functional scale represents a high /healthy level of functioning, a high score for the global health status / QoL represents a high QoL. Patients were assessed up to approx. 8.3 months. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Cycle 1 day 1, cycle 1 day 15, 6 weeks after randomisation and then every 8 weeks until end of treatment

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	571		
Units: Months				
median (confidence interval 95%)	7.10 (6.01 to 9.82)	11.50 (8.80 to 14.32)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 70 months.

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	21.1

Reporting groups

Reporting group title	Placebo@+ fulvestrant

Reporting group description:

Placebo@+ fulvestrant

Reporting group title	BKM120 100 mg@+ fulvestrant

Reporting group description:

BKM120 100 mg@+ fulvestrant

Serious adverse events	Placebo@+ fulvestrant	BKM120 100 mg@+ fulvestrant	
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 570 (17.72%)	146 / 573 (25.48%)	
number of deaths (all causes)	13	12	
number of deaths resulting from adverse events	1	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to central nervous system			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 570 (0.35%)	7 / 573 (1.22%)	
occurrences causally related to treatment / all	0 / 2	3 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Breakthrough pain			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Disease progression			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 570 (0.00%)	7 / 573 (1.22%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	2 / 570 (0.35%)	6 / 573 (1.05%)	
occurrences causally related to treatment / all	0 / 2	5 / 6	
deaths causally related to treatment / all	0 / 1	1 / 1	
Incarcerated hernia			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	2 / 570 (0.35%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 570 (0.53%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 570 (0.53%)	4 / 573 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea at rest			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	8 / 570 (1.40%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 570 (0.00%)	4 / 573 (0.70%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 570 (0.18%)	17 / 573 (2.97%)	
occurrences causally related to treatment / all	0 / 1	15 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 570 (0.18%)	14 / 573 (2.44%)	
occurrences causally related to treatment / all	0 / 1	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 570 (0.18%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			

subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 570 (0.53%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 570 (0.35%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 570 (0.53%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coordination abnormal			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	3 / 570 (0.53%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Dizziness			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemic coma			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 570 (0.35%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 570 (0.70%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 570 (0.53%)	4 / 573 (0.70%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 570 (0.35%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 570 (0.53%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Colitis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 570 (0.35%)	7 / 573 (1.22%)	
occurrences causally related to treatment / all	0 / 2	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 570 (0.35%)	4 / 573 (0.70%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	3 / 570 (0.53%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 570 (0.18%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 570 (0.88%)	7 / 573 (1.22%)	
occurrences causally related to treatment / all	2 / 5	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 570 (0.00%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 570 (0.18%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 570 (0.35%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 570 (0.00%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 570 (0.53%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	3 / 570 (0.53%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cellulitis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 570 (0.00%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 570 (0.00%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	2 / 570 (0.35%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 570 (0.88%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pyelonephritis			
subjects affected / exposed	2 / 570 (0.35%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyuria			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 570 (0.18%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 570 (0.18%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Soft tissue infection			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 570 (0.18%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 570 (0.35%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral labyrinthitis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	0 / 570 (0.00%)	3 / 573 (0.52%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 570 (0.00%)	5 / 573 (0.87%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 570 (0.18%)	2 / 573 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 570 (0.00%)	11 / 573 (1.92%)	
occurrences causally related to treatment / all	0 / 0	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 570 (0.18%)	0 / 573 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 570 (0.00%)	1 / 573 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo@+ fulvestrant	BKM120 100 mg@+ fulvestrant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	485 / 570 (85.09%)	560 / 573 (97.73%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	39 / 570 (6.84%)	229 / 573 (39.97%)	
occurrences (all)	55	280	
Aspartate aminotransferase increased			
subjects affected / exposed	55 / 570 (9.65%)	217 / 573 (37.87%)	
occurrences (all)	76	282	
Blood alkaline phosphatase increased			

subjects affected / exposed	31 / 570 (5.44%)	40 / 573 (6.98%)	
occurrences (all)	36	49	
Gamma-glutamyltransferase increased			
subjects affected / exposed	39 / 570 (6.84%)	45 / 573 (7.85%)	
occurrences (all)	41	54	
Weight decreased			
subjects affected / exposed	24 / 570 (4.21%)	84 / 573 (14.66%)	
occurrences (all)	25	89	
Vascular disorders			
Hot flush			
subjects affected / exposed	53 / 570 (9.30%)	33 / 573 (5.76%)	
occurrences (all)	60	36	
Hypertension			
subjects affected / exposed	29 / 570 (5.09%)	57 / 573 (9.95%)	
occurrences (all)	37	81	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 570 (5.26%)	75 / 573 (13.09%)	
occurrences (all)	34	99	
Dysgeusia			
subjects affected / exposed	22 / 570 (3.86%)	84 / 573 (14.66%)	
occurrences (all)	26	97	
Headache			
subjects affected / exposed	79 / 570 (13.86%)	88 / 573 (15.36%)	
occurrences (all)	112	117	
Tremor			
subjects affected / exposed	7 / 570 (1.23%)	44 / 573 (7.68%)	
occurrences (all)	8	52	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	51 / 570 (8.95%)	38 / 573 (6.63%)	
occurrences (all)	71	52	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	62 / 570 (10.88%)	113 / 573 (19.72%)	
occurrences (all)	75	148	

Fatigue			
subjects affected / exposed	143 / 570 (25.09%)	187 / 573 (32.64%)	
occurrences (all)	167	234	
Injection site pain			
subjects affected / exposed	34 / 570 (5.96%)	27 / 573 (4.71%)	
occurrences (all)	43	35	
Oedema peripheral			
subjects affected / exposed	30 / 570 (5.26%)	38 / 573 (6.63%)	
occurrences (all)	36	49	
Pyrexia			
subjects affected / exposed	22 / 570 (3.86%)	44 / 573 (7.68%)	
occurrences (all)	24	51	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	30 / 570 (5.26%)	40 / 573 (6.98%)	
occurrences (all)	45	47	
Abdominal pain upper			
subjects affected / exposed	38 / 570 (6.67%)	46 / 573 (8.03%)	
occurrences (all)	43	50	
Constipation			
subjects affected / exposed	71 / 570 (12.46%)	68 / 573 (11.87%)	
occurrences (all)	83	90	
Diarrhoea			
subjects affected / exposed	84 / 570 (14.74%)	198 / 573 (34.55%)	
occurrences (all)	111	294	
Dry mouth			
subjects affected / exposed	20 / 570 (3.51%)	46 / 573 (8.03%)	
occurrences (all)	22	49	
Dyspepsia			
subjects affected / exposed	25 / 570 (4.39%)	52 / 573 (9.08%)	
occurrences (all)	27	57	
Nausea			
subjects affected / exposed	138 / 570 (24.21%)	227 / 573 (39.62%)	
occurrences (all)	188	299	
Stomatitis			

subjects affected / exposed	40 / 570 (7.02%)	124 / 573 (21.64%)	
occurrences (all)	43	166	
Vomiting			
subjects affected / exposed	79 / 570 (13.86%)	92 / 573 (16.06%)	
occurrences (all)	123	116	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	69 / 570 (12.11%)	76 / 573 (13.26%)	
occurrences (all)	78	91	
Dyspnoea			
subjects affected / exposed	56 / 570 (9.82%)	44 / 573 (7.68%)	
occurrences (all)	67	52	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	20 / 570 (3.51%)	41 / 573 (7.16%)	
occurrences (all)	22	47	
Dry skin			
subjects affected / exposed	17 / 570 (2.98%)	69 / 573 (12.04%)	
occurrences (all)	21	77	
Pruritus			
subjects affected / exposed	33 / 570 (5.79%)	88 / 573 (15.36%)	
occurrences (all)	41	116	
Rash			
subjects affected / exposed	39 / 570 (6.84%)	187 / 573 (32.64%)	
occurrences (all)	46	273	
Rash maculo-papular			
subjects affected / exposed	8 / 570 (1.40%)	39 / 573 (6.81%)	
occurrences (all)	8	48	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	53 / 570 (9.30%)	129 / 573 (22.51%)	
occurrences (all)	64	164	
Depression			
subjects affected / exposed	56 / 570 (9.82%)	152 / 573 (26.53%)	
occurrences (all)	75	202	
Insomnia			

subjects affected / exposed	50 / 570 (8.77%)	60 / 573 (10.47%)	
occurrences (all)	51	62	
Mood altered			
subjects affected / exposed	17 / 570 (2.98%)	40 / 573 (6.98%)	
occurrences (all)	18	43	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	74 / 570 (12.98%)	62 / 573 (10.82%)	
occurrences (all)	102	75	
Back pain			
subjects affected / exposed	72 / 570 (12.63%)	66 / 573 (11.52%)	
occurrences (all)	89	78	
Bone pain			
subjects affected / exposed	34 / 570 (5.96%)	38 / 573 (6.63%)	
occurrences (all)	41	44	
Muscle spasms			
subjects affected / exposed	21 / 570 (3.68%)	32 / 573 (5.58%)	
occurrences (all)	23	41	
Musculoskeletal pain			
subjects affected / exposed	40 / 570 (7.02%)	27 / 573 (4.71%)	
occurrences (all)	48	30	
Pain in extremity			
subjects affected / exposed	61 / 570 (10.70%)	51 / 573 (8.90%)	
occurrences (all)	81	66	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	31 / 570 (5.44%)	29 / 573 (5.06%)	
occurrences (all)	34	31	
Urinary tract infection			
subjects affected / exposed	31 / 570 (5.44%)	46 / 573 (8.03%)	
occurrences (all)	40	60	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	68 / 570 (11.93%)	174 / 573 (30.37%)	
occurrences (all)	74	208	
Hyperglycaemia			

subjects affected / exposed	46 / 570 (8.07%)	244 / 573 (42.58%)	
occurrences (all)	81	408	
Hypokalaemia			
subjects affected / exposed	13 / 570 (2.28%)	41 / 573 (7.16%)	
occurrences (all)	21	56	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2013	1) A higher than expected rate of patients were randomized with PI3K pathway status unknown (approximately 25% as compared to initial assumptions of 10%). Study design, primary endpoints, statistical and biomarker sections were modified due to higher incidence of the unknown PI3K pathway status patients, and to mitigate the impact on the overall analysis. 2) In addition, futility rule at interim look was modified to be more aggressive in order to increase the probability to stop the study at the interim look if the null hypothesis based on the Main study cohort was true, while maintaining a good level of power; PK analysis was clarified and modifications to the management of psychiatric disorders (follow up advisory board), stomatitis and rash were made. 3) PI3K pathway activation status (one of the two stratification factors) definition was modified to exclude PTEN gene mutation (exon 4). Considering the very small number of ER+ breast cancer patients expected to display mutation of the PTEN gene (<2%) this analysis was performed in an exploratory fashion. 4) In view of positive data published on the potential utility for circulating DNA to detect mutations in the PI3K related pathway genes in MBC, blood collection at entry on study for mutation analysis in circulating DNA was made mandatory. 5) Clarifications were made with respect to PK analysis and modifications to the management of psychiatric disorders (follow up advisory board), stomatitis and rash were made. 6) Other changes for clarification purpose included pregnancy testing requirement, definition of post-menopausal status, fulvestrant discontinuation criteria, ECG parameters, protocol window for signed informed consent and shipment of tumor sample, as well as editorial changes.
30 May 2013	1) To update and align the management of selected AEs across the buparlisib program (e.g. transaminases increase, grade 2 hyperglycemia). 2) To increase the AEs recovery time period by increasing the maximum allowed treatment interruption for buparlisib/placebo from 21 to 28 days. 3) Weekly monitoring of hematology and partial biochemistry parameters (AST/SGOT, ALT/SGPT, alkaline phosphatase, total bilirubin and creatinine) during the first two cycles of study treatment starting from Cycle 1 Day 15 to allow early patients safety management. 4) Changes in eligibility criteria, inclusion criteria were revised to: * Allow inclusion of patients with prior documentation of PI3K pathway results through a Novartis central laboratory and adequate tumor tissue. * Clarify that postmenopausal range for hormone levels was either serum FSH >40 mIU/mL and estradiaol <20 pg/mL, or according to the respective postmenopausal range definition used by the local laboratory involved. * Allow patients with AST/ALT/total bilirubin values below to the lower limit of normal because these patients were suitable to participate in the study. 5) The PI3K pathway activation status definition was modified and no longer included PIK3CA mutations in exon 5 which were very rare in breast cancer. 6) Time to deterioration of ECOG performance status was added as a secondary objective to support the assessment of clinical benefit.

31 July 2014	The amendment ensured the generalizability of the results to the entire randomized population. 1) Full population was defined as Main study cohort + PI3K unknown cohort, 2) The primary hypothesis of interest was modified with the addition of PFS and OS in Full population as primary and key-secondary endpoints. There were three populations of interest: i) Main cohort and/or ii) Full population or iii) PI3K activated subpopulation, 3) The gatekeeping procedure was modified so that a formal statistical test can be used to test PFS/OS in the Full population, 4) The final OS analysis will be driven by the observed number of deaths in the Full population, 5) The ORR, CBR, ECOG, HRQoL analysis will also be done in the Full population. In addition following changes were made: 1) Clarification was provided that at the time of final PFS analyses, both PFS and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at the interim analyses). 2) Collection of blood samples for CTCs was stopped in the study at Baseline and following treatment (Cycle 3 Day 1) for an exploratory analysis. 3) Co-administration of weak and moderate inducers and inhibitors with buparlisib was permitted during the course of the study as per the Investigator’s Brochure (version 6). Strong inhibitors and inducers remain prohibited. 4) Moderate doses of corticosteroids equivalent to up to 4 mg once daily of dexamethasone were allowed. 5) Changes in safety management were made as per Investigator’s Brochure (version 6).
23 July 2015	1) Additional guidance was provided to Investigators around management of liver toxicity: During the search for potential drug-induced liver injury (DILI) cases in buparlisib Novartis-sponsored trials, few cases of DILI cases were consistent with the Hy’s law criteria. Hence the liver-related safety measures were updated in ongoing protocols to enhance patient safety. 2) Clarification was provided for, study treatment discontinuation, lost to follow-up, and withdrawal of consent. 3) Clarification for requirements for efficacy, safety and patient-reported outcomes (PRO) assessments were provided after final PFS analysis.
22 June 2016	The key features of this amendment were: 1) Provided a clarification on the measures to follow when a patient exhibited suicidal ideation regardless of the response to question 9 of the Patient Health Questionnaire (PHQ-9) questionnaire. 2) After the final OS analysis, unblinding occurred. The frequency of study evaluations was reduced and standard of care was followed while maintaining the key safety assessments. The patients continued to receive treatment with buparlisib and/or fulvestrant until either progression of disease, unacceptable toxicities, withdrawal of patient consent, physician decision or discontinuation of buparlisib development by Novartis, whichever occurred earlier. Patients considered to be benefiting from study treatment per investigator assessment could be eligible to continue to receive study treatment. 3) After the final OS analysis, tumor evaluation was performed as per standard of care and survival follow up was not performed.

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.

Novartis made the decision not to pursue further development of buparlisib and to terminate the ongoing studies in Breast Cancer. The CBKM120F2302 study was terminated on 19-Apr-2019 (last subject last visit).

Notes: