Clinical trial results:
Phase II Randomized Double-Blind Placebo-Controlled Trial of Combination of Pimasertib with SAR245409 or of Pimasertib with SAR245409 Placebo in Subjects with Previously Treated Unresectable Low-Grade Ovarian Cancer

Summary

EudraCT number	2013-000902-40
Trial protocol	IT BE ES PL
Global end of trial date	30 November 2017

Results information

Result version number	v1 (current)
This version publication date	13 December 2018
First version publication date	13 December 2018

Trial information

Trial identification

Sponsor protocol code	EMR200066_012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01936363
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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	30 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate whether the objective tumor response of the combination therapy with pimasertib plus SAR245409 is superior to that of pimasertib plus SAR245409 placebo in subjects with previously treated unresectable low grade ovarian carcinoma according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as determined by the Investigator.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2013
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	Australia: 8
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	65
EEA total number of subjects	19

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)	53
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Sep 2013/Oct 2014. Clinical data cut off: Jan 2018.

Pre-assignment

Screening details:

Total 75 subjects were screened for this trial. Out of those subjects, 65 subjects were randomized to treatment in this trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Pimasertib (Once Daily) Plus SAR245409

Arm description:

Subejcts received Pimasertib oral capsule at a dose of 60 milligram (mg) once daily along with SAR245409 oral capsule at a dose of 70 mg once daily and placebo matched to pimasertib in evening until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

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

Dosage and administration details:

Pimasertib oral capsule at a dose of 60 milligram (mg) administered once daily until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Investigational medicinal product name	SAR245409
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SAR245409 oral capsule at a dose of 70 mg administered once daily until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Investigational medicinal product name	Placebo matched pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched pimasertib oral capsule at a dose of 60 mg administered once daily in evening until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Arm title	Pimasertib (Twice Daily) Plus SAR245409 Placebo

Arm description:

Subjects received pimasertib oral capsule at a dose of 60 mg twice daily along with placebo matched to

SAR245409 once daily in morning until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

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

Dosage and administration details:

Pimasertib oral capsule at a dose of 60 mg administered twice daily until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Investigational medicinal product name	Placebo matched SAR245409
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched SAR245409 administered once daily in morning until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Number of subjects in period 1	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo
Started	32	33
Completed	32	33

Baseline characteristics

Reporting groups	
Reporting group title	Pimasertib (Once Daily) Plus SAR245409
Reporting group description:	
Subejcts received Pimasertib oral capsule at a dose of 60 milligram (mg) once daily along with SAR245409 oral capsule at a dose of 70 mg once daily and placebo matched to pimasertib in evening until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.	
Reporting group title	Pimasertib (Twice Daily) Plus SAR245409 Placebo
Reporting group description:	
Subjects received pimasertib oral capsule at a dose of 60 mg twice daily along with placebo matched to SAR245409 once daily in morning until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.	

Reporting group values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo	Total
Number of subjects	32	33	65
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	47.3	50.6	
standard deviation	± 14.07	± 16.39	-
Gender, Male/Female Units: Subjects			
Female	32	33	65
Male	0	0	0

End points

End points reporting groups

Reporting group title	Pimasertib (Once Daily) Plus SAR245409

Reporting group description:

Subejcts received Pimasertib oral capsule at a dose of 60 milligram (mg) once daily along with SAR245409 oral capsule at a dose of 70 mg once daily and placebo matched to pimasertib in evening until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Reporting group title	Pimasertib (Twice Daily) Plus SAR245409 Placebo

Reporting group description:

Subjects received pimasertib oral capsule at a dose of 60 mg twice daily along with placebo matched to SAR245409 once daily in morning until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Primary: Objective Tumor Response

End point title	Objective Tumor Response[1]

End point description:

Objective tumor response was defined as the presence of at least one Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to more than (<) 10 millimeter (mm). Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Intent-to Treat (ITT) analysis set included all subjects who had been randomized.

End point type	Primary

End point timeframe:

From randomization until disease progression or death assessed every 8 weeks up to week 32, and thereafter every 12 weeks up to 52 months

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: Only descriptive statistics were reported.

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: percentage of subjects				
number (confidence interval 95%)	12.5 (3.5 to 29.0)	12.1 (3.4 to 28.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

PFS: time from randomization to first documentation of objective tumor progression.CR:Disappearance of all target lesions.Any pathological lymph nodes(whether target or non-target)must have reduction in short axis to<10 mm.PR:At least 30% decrease in sum of diameters of target lesions,taking as reference baseline sum diameters.PD:At least a 20% increase in sum of diameters of target lesions,taking as reference smallest sum on study.In addition to relative increase of 20%,the sum also demonstrate absolute increase of at least 5 mm.SD:Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD,taking as reference smallest sum diameters while on study. Median PFS was computed using Kaplan-Meier estimates (product-limit estimates) and was presented with 95% confidence interval. ITT analysis set used. Here 99999=upper limit of 95% Confidence Interval for PFS could not be calculated because this upper limit was not reached due to limited number of events.

End point type	Secondary

End point timeframe:

Time from randomization until first observation of progressive disease or death, assessed up to 52 months

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: months				
median (confidence interval 95%)	9.99 (3.42 to 15.21)	12.71 (4.21 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Control

End point title	Percentage of Subjects With Disease Control

End point description:

Disease control as per RECIST v.1.1 was defined as the proportion of subjects with stable disease (SD), for at least 16 weeks, PR or CR according to RECIST v1.1 criteria. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PD: At least a 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters). CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. ITT analysis set included all subjects who had been randomized.

End point type	Secondary

End point timeframe:

Randomization until disease progression or death assessed every 8 weeks up to week 32, and thereafter every 12 weeks up to 52 months

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: percentage of subjects				
number (confidence interval 95%)	50.0 (31.9 to 68.1)	39.4 (22.9 to 57.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the time (in months) from randomization to death. Data has been presented in terms of number of subjects who died and number of censored subjects. ITT analysis set included all subjects who had been randomized.

End point type	Secondary

End point timeframe:

Time from randomization until death, assessed up to 52 months

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: subjects				
Number of deaths|	8	6		
Number for censored|	24	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HrQoL) assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)

End point title	Health Related Quality of Life (HrQoL) assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30: 30-item questionnaire comprising of five functional scales(physical, role, cognitive,

emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact) and a global quality of life (QoL) scale summarized from two 7-point scales (overall QoL and overall general health).Each of multi-item scales includes a different set of items-no item occurs in more than one scale.All of the scales and individual single-items ranged in score from 0 to 100.A high scale score=higher response level.High score for a functional scale=high/healthy level of functioning, a high score for the global health status/ QoL=high QoL, but a high score for a symptom scale/item=high level of symptomatology/problems. Data was not collected for this endpoint because as per Protocol Amendment4 (13 March 2015),collection of patient-reported health-related quality of life outcomes was discontinued.

End point type	Secondary

End point timeframe:

Baseline up to disease progression or withdrawal, assessed up to 52 months

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: units on scale				

Notes:

[2] - Data was not collected due to the reason provided in description.

[3] - Data was not collected due to the reason provided in description.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HrQoL) Assessed Using European Organization for Research and Treatment of Cancer (EORTC) Ovarian-Specific Module Quality of Life Questionnaire Ovarian Cancer Module (QLQ-OV28)

End point title	Health Related Quality of Life (HrQoL) Assessed Using European Organization for Research and Treatment of Cancer (EORTC) Ovarian-Specific Module Quality of Life Questionnaire Ovarian Cancer Module (QLQ-OV28)

End point description:

EORTC QLQ-OV28 assesses disease and treatment-related symptoms of ovarian cancer. The 28-item module comprises of 6 symptom scales (abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal symptoms, body image, attitude to disease and treatment), and sexual functioning. All of the scales and the individual single-items ranged in score from 0 to 100. Higher scores indicate a better quality of life. Data was not collected for this outcome because as per Protocol Amendment 4 (dated 13 March 2015), the collection of patient-reported health-related quality of life outcomes was discontinued.

End point type	Secondary

End point timeframe:

Baseline up to disease progression or withdrawal, assessed up to 52 months

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: units on scale				

Notes:

[4] - Data was not collected due to the reason provided in description.

[5] - Data was not collected due to the reason provided in description.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Discontinuation of Treatment and Death

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Discontinuation of Treatment and Death

End point description:

TEAEs, Serious TEAEs and AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0. An adverse event was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A Serious Adverse Event was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to data cut-off that were absent before treatment or that worsened relative to pretreatment state. Safety population (SAF) analysis set included all subjects who received at least one dose of any trial treatment.

End point type	Secondary

End point timeframe:

First dose of study drug up to 52 months

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: subjects				
TEAE	32	32		
Serious TEAE	16	18		
TEAE leading to discontinuation of study treatment	16	12		
Death	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) After Dose of pimasertib and SAR245409

End point title	Maximum Plasma Concentration (Cmax) After Dose of pimasertib and SAR245409

End point description:

As per changed in planned analysis the endpoint related to pharmacokinetic parameters was not assessed.

End point type	Secondary

End point timeframe:

Pre-dose Hour 0.5, 1.5, 4.5 8 post dose on Day 15, 29, 43

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - Data was not assessed as per change in planned analysis.

[7] - Data was not assessed as per change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve (AUC) After Dose of pimasertib and SAR245409

End point title	Area under the curve (AUC) After Dose of pimasertib and SAR245409

End point description:

As per changed in planned analysis the outcome measure related to pharmacokinetic parameters was not assessed.

End point type	Secondary

End point timeframe:

Pre-dose Hour 0.5, 1.5, 4.5 8 post dose on Day 15, 29, 43

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: mg*min/dL				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - Data was not assessed as per change in planned analysis.

[9] - Data was not assessed as per change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular Alterations in MAPK and/or PI3K Signaling Pathway Components/Modulators in Tumor Tissue and Blood

End point title	Molecular Alterations in MAPK and/or PI3K Signaling Pathway Components/Modulators in Tumor Tissue and Blood

End point description:

As per changed in planned analysis the outcome measure related to pharmacodynamics parameters was not assessed.

End point type	Secondary

End point timeframe:

Screening visit (day -28 to 1)

End point values	Pimasertib (Once Daily) Plus SAR245409	Pimasertib (Twice Daily) Plus SAR245409 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Not available				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - Data was not assessed as per change in planned analysis.

[11] - Data was not assessed as per change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to 52 months

Adverse event reporting additional description:

SAF for "Pimasertib (Once Daily) Plus SAR245409" = 32 subjects and "Pimasertib (Twice Daily) Plus SAR245409 Placebo" = 32 subjects. Adverse events analysis was based on the SAF which includes 64 subjects. One subject was randomized by error and not treated therefore adverse event analysis was not performed.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Pimasertib (Twice Daily) Plus SAR245409 Placebo

Reporting group description:

subjects received pimasertib oral capsule at a dose of 60 mg twice daily along with placebo matched SAR245409 once daily in morning until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Reporting group title	Pimasertib (Once Daily) Plus SAR245409

Reporting group description:

subjects received Pimasertib oral capsule at a dose of 60 milligram (mg) once daily along with SAR245409 oral capsule at a dose of 70 mg once daily and placebo matched pimasertib in evening until disease progression, death, intolerable toxicity or withdrawal of informed consent, whichever came first.

Serious adverse events	Pimasertib (Twice Daily) Plus SAR245409 Placebo	Pimasertib (Once Daily) Plus SAR245409	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 32 (56.25%)	16 / 32 (50.00%)	
number of deaths (all causes)	6	8	
number of deaths resulting from adverse events			
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (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	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cough			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Aspiration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			

subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding tube complication			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 32 (12.50%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			

subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
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 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic kidney disease			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (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 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (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 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (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			
Cellulitis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritonitis bacterial			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			

subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acidosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
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	Pimasertib (Twice Daily) Plus SAR245409 Placebo	Pimasertib (Once Daily) Plus SAR245409	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	32 / 32 (100.00%)	
Vascular disorders			
Hypertension			

subjects affected / exposed	4 / 32 (12.50%)	3 / 32 (9.38%)	
occurrences (all)	4	3	
Deep vein thrombosis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 32 (43.75%)	19 / 32 (59.38%)	
occurrences (all)	14	19	
Oedema peripheral			
subjects affected / exposed	15 / 32 (46.88%)	11 / 32 (34.38%)	
occurrences (all)	15	11	
Pyrexia			
subjects affected / exposed	8 / 32 (25.00%)	6 / 32 (18.75%)	
occurrences (all)	8	6	
Chills			
subjects affected / exposed	2 / 32 (6.25%)	9 / 32 (28.13%)	
occurrences (all)	2	9	
Asthenia			
subjects affected / exposed	8 / 32 (25.00%)	0 / 32 (0.00%)	
occurrences (all)	8	0	
Face oedema			
subjects affected / exposed	3 / 32 (9.38%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Peripheral swelling			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Influenza like illness			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Mucosal inflammation			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Malaise			

subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Mass			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Vulvovaginal dryness			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 32 (12.50%)	8 / 32 (25.00%)	
occurrences (all)	4	8	
Dyspnoea			
subjects affected / exposed	6 / 32 (18.75%)	7 / 32 (21.88%)	
occurrences (all)	6	7	
Dyspnoea exertional			
subjects affected / exposed	3 / 32 (9.38%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
Epistaxis			
subjects affected / exposed	1 / 32 (3.13%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Nasal congestion			
subjects affected / exposed	1 / 32 (3.13%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Oropharyngeal pain			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 32 (0.00%)	5 / 32 (15.63%)	
occurrences (all)	0	5	
Insomnia			

subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	19 / 32 (59.38%)	19 / 32 (59.38%)	
occurrences (all)	19	19	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 32 (12.50%)	7 / 32 (21.88%)	
occurrences (all)	4	7	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 32 (9.38%)	7 / 32 (21.88%)	
occurrences (all)	3	7	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 32 (0.00%)	4 / 32 (12.50%)	
occurrences (all)	0	4	
Weight increased			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Neutrophil count decreased			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Fall			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	

Tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 32 (21.88%)	11 / 32 (34.38%)	
occurrences (all)	7	11	
Headache			
subjects affected / exposed	6 / 32 (18.75%)	3 / 32 (9.38%)	
occurrences (all)	6	3	
Paraesthesia			
subjects affected / exposed	2 / 32 (6.25%)	5 / 32 (15.63%)	
occurrences (all)	2	5	
Dysgeusia			
subjects affected / exposed	3 / 32 (9.38%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Migraine			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Syncope			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Hypoaesthesia			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Lethargy			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Tremor			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	5 / 32 (15.63%)	7 / 32 (21.88%)	
occurrences (all)	5	7	
Anaemia of chronic disease			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Eye disorders			
Vision blurred			
subjects affected / exposed	11 / 32 (34.38%)	16 / 32 (50.00%)	
occurrences (all)	11	16	
Macular detachment			
subjects affected / exposed	5 / 32 (15.63%)	6 / 32 (18.75%)	
occurrences (all)	5	6	
Visual impairment			
subjects affected / exposed	3 / 32 (9.38%)	7 / 32 (21.88%)	
occurrences (all)	3	7	
Retinal detachment			
subjects affected / exposed	6 / 32 (18.75%)	3 / 32 (9.38%)	
occurrences (all)	6	3	
Eyelid oedema			
subjects affected / exposed	4 / 32 (12.50%)	2 / 32 (6.25%)	
occurrences (all)	4	2	
Subretinal fluid			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Visual acuity reduced			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Eye disorder			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Periorbital oedema			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Dry eye			

subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	26 / 32 (81.25%)	26 / 32 (81.25%)	
occurrences (all)	26	26	
Nausea			
subjects affected / exposed	13 / 32 (40.63%)	22 / 32 (68.75%)	
occurrences (all)	13	22	
Vomiting			
subjects affected / exposed	14 / 32 (43.75%)	16 / 32 (50.00%)	
occurrences (all)	14	16	
Stomatitis			
subjects affected / exposed	9 / 32 (28.13%)	13 / 32 (40.63%)	
occurrences (all)	9	13	
Abdominal pain			
subjects affected / exposed	8 / 32 (25.00%)	8 / 32 (25.00%)	
occurrences (all)	8	8	
Constipation			
subjects affected / exposed	5 / 32 (15.63%)	6 / 32 (18.75%)	
occurrences (all)	5	6	
Dry mouth			
subjects affected / exposed	3 / 32 (9.38%)	8 / 32 (25.00%)	
occurrences (all)	3	8	
Abdominal distension			
subjects affected / exposed	2 / 32 (6.25%)	6 / 32 (18.75%)	
occurrences (all)	2	6	
Dyspepsia			
subjects affected / exposed	4 / 32 (12.50%)	5 / 32 (15.63%)	
occurrences (all)	4	5	
Abdominal pain upper			
subjects affected / exposed	3 / 32 (9.38%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	

Proctalgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Abdominal pain lower			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Cheilitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Hypoaesthesia oral			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	19 / 32 (59.38%)	12 / 32 (37.50%)	
occurrences (all)	19	12	
Dry skin			
subjects affected / exposed	11 / 32 (34.38%)	9 / 32 (28.13%)	
occurrences (all)	11	9	
Alopecia			
subjects affected / exposed	4 / 32 (12.50%)	12 / 32 (37.50%)	
occurrences (all)	4	12	
Rash			
subjects affected / exposed	9 / 32 (28.13%)	6 / 32 (18.75%)	
occurrences (all)	9	6	
Rash maculo-papular			
subjects affected / exposed	5 / 32 (15.63%)	7 / 32 (21.88%)	
occurrences (all)	5	7	
Pruritus			
subjects affected / exposed	4 / 32 (12.50%)	8 / 32 (25.00%)	
occurrences (all)	4	8	
Erythema			
subjects affected / exposed	0 / 32 (0.00%)	4 / 32 (12.50%)	
occurrences (all)	0	4	
Skin fissures			

subjects affected / exposed	3 / 32 (9.38%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Acne			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Hyperhidrosis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	9	2	
Hypertrichosis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 32 (0.00%)	4 / 32 (12.50%)	
occurrences (all)	0	4	
Haematuria			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	7 / 32 (21.88%)	9 / 32 (28.13%)	
occurrences (all)	7	9	
Arthralgia			
subjects affected / exposed	2 / 32 (6.25%)	7 / 32 (21.88%)	
occurrences (all)	2	7	
Muscular weakness			
subjects affected / exposed	1 / 32 (3.13%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Pain in extremity			
subjects affected / exposed	2 / 32 (6.25%)	4 / 32 (12.50%)	
occurrences (all)	2	4	
Back pain			

subjects affected / exposed	1 / 32 (3.13%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Muscle spasms			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 32 (25.00%)	5 / 32 (15.63%)	
occurrences (all)	8	5	
Conjunctivitis			
subjects affected / exposed	3 / 32 (9.38%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Rash pustular			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Cellulitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 32 (18.75%)	11 / 32 (34.38%)	
occurrences (all)	6	11	
Hypomagnesaemia			
subjects affected / exposed	4 / 32 (12.50%)	5 / 32 (15.63%)	
occurrences (all)	4	5	
Dehydration			

subjects affected / exposed	3 / 32 (9.38%)	5 / 32 (15.63%)	
occurrences (all)	3	5	
Hypokalaemia			
subjects affected / exposed	6 / 32 (18.75%)	3 / 32 (9.38%)	
occurrences (all)	6	3	
Hypoalbuminaemia			
subjects affected / exposed	3 / 32 (9.38%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
Hypocalcaemia			
subjects affected / exposed	4 / 32 (12.50%)	1 / 32 (3.13%)	
occurrences (all)	4	1	
Glucose tolerance impaired			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2013	1- Included "Benefits and Risks Assessment" section. 2- Extended the period for using an adequate method of contraception after discontinuation of trial medication. 3- Extended the reporting period of adverse events for female subjects.
03 July 2014	The purpose of this amendment was to make the following updates: 1- Amend the inclusion and exclusion criteria. 2- Extend the period for using an adequate method of contraception after discontinuation of trial treatment. 3- Clarify the creatine phosphokinase (CPK) criterion for withdrawal of the trial treatment. 4- Amend the guidance for the monitoring and recording of AEs. 5- Introduce further guidance on trial treatment modifications and amend the management of specific trial treatment related AEs. 6- Clarify the assessment of pharmacogenetics (PGx) and biomarkers and to specify informed consent procedures for the collection of PGx samples. 7- Add an administrative interim analysis. 8- Clarify instructions for the collection of tumor tissue samples and initial stratification based on histology. 9- Specify that the corrected QT interval will be calculated using Fredericia's formula. 10- Clarify the list of prohibited medicines.
14 November 2014	The purpose of this amendment was to make the following updates: 1- Include a newly planned futility analysis, including the scope of analysis and related parameters such as number of subjects included in the futility analysis and impact on power of primary analysis. 2- Introduce the temporary enrollment stop between at least 50 subjects being enrolled and the conclusions derived from the outcome of the futility analysis. 3- Update the end of trial definition.
13 March 2015	The purpose of this amendment was to make the following updates: 1- Update the overall trial design to allow subjects to continue treatment, however, for subjects who had a placebo component for their treatment assignment, placebo was to be withdrawn after approval of this amendment. 2- Modify the planned trial period (first enrollment-last subject out). 3- Modify the primary and secondary endpoint analyses. 4- Modify collection of subject data and endpoint analysis. 5- Provide information to the Investigator on awareness of dehydration and renal failure secondary to gastrointestinal toxicity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported