



**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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**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:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| 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 |
|------------------------------|-----|

|                  |  |
|------------------|--|
| <b>Arm title</b> | Pimasertib (Once Daily) Plus SAR245409 |
|------------------|--|

Arm 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 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.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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:

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 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<br>Units: Subjects |  |   |       |

|   |                 |                 |    |
|---|-----------------|-----------------|----|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 47.3<br>± 14.07 | 50.6<br>± 16.39 | -  |
| Gender, Male/Female<br>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:

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 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 <sup>[1]</sup> |
|-----------------|---|

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 |
|-----------------|---------------------------|

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**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.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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**End point timeframe:**

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

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| <b>End point values</b>          | 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)                           |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Percentage of Subjects With Disease Control**

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|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Disease Control |
|-----------------|---|

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**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.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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**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

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|                                  |   |   |  |  |
|----------------------------------|---|---|--|--|
| <b>End point values</b>          | Pimasertib<br>(Once Daily)<br>Plus<br>SAR245409 | Pimasertib<br>(Twice Daily)<br>Plus<br>SAR245409<br>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<br>68.1)                          | 39.4 (22.9 to<br>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   |                  |

|                             |   |   |  |  |
|-----------------------------|---|---|--|--|
| <b>End point values</b>     | Pimasertib<br>(Once Daily)<br>Plus<br>SAR245409 | Pimasertib<br>(Twice Daily)<br>Plus<br>SAR245409<br>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 Amendment 4 (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

| <b>End point values</b>     | Pimasertib (Once Daily) Plus SAR245409 | Pimasertib (Twice Daily) Plus SAR245409 Placebo |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                        | Reporting group                                 |  |  |
| Number of subjects analysed | 0 <sup>[2]</sup>                       | 0 <sup>[3]</sup>                                |  |  |
| 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

|                             |   |   |  |  |
|-----------------------------|---|---|--|--|
| <b>End point values</b>     | Pimasertib<br>(Once Daily)<br>Plus<br>SAR245409 | Pimasertib<br>(Twice Daily)<br>Plus<br>SAR245409<br>Placebo |  |  |
| Subject group type          | Reporting group                                 | Reporting group   |  |  |
| Number of subjects analysed | 0 <sup>[4]</sup>                                | 0 <sup>[5]</sup>  |  |  |
| 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

|  |   |   |  |  |
|--|---|---|--|--|
| <b>End point values</b>                            | Pimasertib<br>(Once Daily)<br>Plus<br>SAR245409 | Pimasertib<br>(Twice Daily)<br>Plus<br>SAR245409<br>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 <sup>[6]</sup>                       | 0 <sup>[7]</sup>                                |  |  |
| 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 <sup>[8]</sup>                       | 0 <sup>[9]</sup>                                |  |  |
| 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 <sup>[10]</sup>                      | 0 <sup>[11]</sup>                               |  |  |
| 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.

| <b>Serious adverse events</b>                     | 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          |  |
| <b>Stomatitis</b>                               |                |                |  |
| 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          |  |
| <b>Subileus</b>                                 |                |                |  |
| 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          |  |
| <b>Hepatobiliary disorders</b>                  |                |                |  |
| 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          |  |
| <b>Skin and subcutaneous tissue disorders</b>   |                |                |  |
| 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          |  |
| <b>Renal and urinary disorders</b>              |                |                |  |
| 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          |  |
| <b>Metabolism and nutrition disorders</b>       |                |                |  |
| <b>Dehydration</b>                              |                |                |  |
| 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          |  |
| <b>Acidosis</b>                                 |                |                |  |
| 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          |  |
| <b>Hypokalaemia</b>                             |                |                |  |
| 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          |  |
| <b>Hyponatraemia</b>                            |                |                |  |
| 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          |  |
| <b>Hypophosphataemia</b>                        |                |                |  |
| 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 %

| <b>Non-serious adverse events</b>                     | 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%)                      |  |
| <b>Vascular disorders</b>                             |   |  |  |
| 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                |  |
| <b>General disorders and administration site conditions</b> |                  |                  |  |
| 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<br>occurrences (all)   | 0 / 32 (0.00%)<br>0  | 2 / 32 (6.25%)<br>2  |  |
| Mass<br>subjects affected / exposed<br>occurrences (all)   | 0 / 32 (0.00%)<br>0  | 2 / 32 (6.25%)<br>2  |  |
| Reproductive system and breast disorders<br>Pelvic pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 32 (0.00%)<br>0  | 2 / 32 (6.25%)<br>2  |  |
| Vulvovaginal dryness<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 32 (0.00%)<br>0  | 2 / 32 (6.25%)<br>2  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 4 / 32 (12.50%)<br>4 | 8 / 32 (25.00%)<br>8 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 6 / 32 (18.75%)<br>6 | 7 / 32 (21.88%)<br>7 |  |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 32 (9.38%)<br>3  | 3 / 32 (9.38%)<br>3  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 32 (3.13%)<br>1  | 4 / 32 (12.50%)<br>4 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 32 (3.13%)<br>1  | 4 / 32 (12.50%)<br>4 |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 32 (0.00%)<br>0  | 3 / 32 (9.38%)<br>3  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 32 (0.00%)<br>0  | 5 / 32 (15.63%)<br>5 |  |
| Insomnia   |                      |                      |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)      | 1 / 32 (3.13%)<br>1 | 2 / 32 (6.25%)<br>2 |  |
| <b>Investigations</b>                                 |                     |                     |  |
| 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                   |  |
| <b>Injury, poisoning and procedural complications</b> |                     |                     |  |
| 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                   |  |
| <b>Cardiac disorders</b>                              |                     |                     |  |
| 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                |  |
| <b>Nervous system disorders</b>             |                 |                  |  |
| 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                |  |
| <b>Blood and lymphatic system disorders</b> |                 |                  |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| 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<br>occurrences (all) | 0 / 32 (0.00%)<br>0    | 2 / 32 (6.25%)<br>2    |  |
| <b>Gastrointestinal disorders</b>                |                        |                        |  |
| <b>Diarrhoea</b>                                 |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 26 / 32 (81.25%)<br>26 | 26 / 32 (81.25%)<br>26 |  |
| <b>Nausea</b>                                    |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 13 / 32 (40.63%)<br>13 | 22 / 32 (68.75%)<br>22 |  |
| <b>Vomiting</b>                                  |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 14 / 32 (43.75%)<br>14 | 16 / 32 (50.00%)<br>16 |  |
| <b>Stomatitis</b>                                |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 9 / 32 (28.13%)<br>9   | 13 / 32 (40.63%)<br>13 |  |
| <b>Abdominal pain</b>                            |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 32 (25.00%)<br>8   | 8 / 32 (25.00%)<br>8   |  |
| <b>Constipation</b>                              |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 32 (15.63%)<br>5   | 6 / 32 (18.75%)<br>6   |  |
| <b>Dry mouth</b>                                 |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 32 (9.38%)<br>3    | 8 / 32 (25.00%)<br>8   |  |
| <b>Abdominal distension</b>                      |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 32 (6.25%)<br>2    | 6 / 32 (18.75%)<br>6   |  |
| <b>Dyspepsia</b>                                 |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 32 (12.50%)<br>4   | 5 / 32 (15.63%)<br>5   |  |
| <b>Abdominal pain upper</b>                      |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 32 (9.38%)<br>3    | 1 / 32 (3.13%)<br>1    |  |
| <b>Gastrooesophageal reflux disease</b>          |                        |                        |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 32 (3.13%)<br>1    | 2 / 32 (6.25%)<br>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<br>occurrences (all)   | 3 / 32 (9.38%)<br>3  | 1 / 32 (3.13%)<br>1  |  |
| Acne<br>subjects affected / exposed<br>occurrences (all)   | 1 / 32 (3.13%)<br>1  | 2 / 32 (6.25%)<br>2  |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 32 (0.00%)<br>9  | 2 / 32 (6.25%)<br>2  |  |
| Hypertrichosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 32 (0.00%)<br>0  | 2 / 32 (6.25%)<br>2  |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 32 (0.00%)<br>0  | 4 / 32 (12.50%)<br>4 |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>2  | 1 / 32 (3.13%)<br>1  |  |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 32 (6.25%)<br>2  | 0 / 32 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>Myalgia<br>subjects affected / exposed<br>occurrences (all) | 7 / 32 (21.88%)<br>7 | 9 / 32 (28.13%)<br>9 |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>2  | 7 / 32 (21.88%)<br>7 |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 32 (3.13%)<br>1  | 4 / 32 (12.50%)<br>4 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 2 / 32 (6.25%)<br>2  | 4 / 32 (12.50%)<br>4 |  |
| Back pain  |                      |                      |  |

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 24 October 2013  | <ol style="list-style-type: none"><li>1- Included "Benefits and Risks Assessment" section.</li><li>2- Extended the period for using an adequate method of contraception after discontinuation of trial medication.</li><li>3- Extended the reporting period of adverse events for female subjects.</li></ol>  |
| 03 July 2014     | <p>The purpose of this amendment was to make the following updates:</p> <ol style="list-style-type: none"><li>1- Amend the inclusion and exclusion criteria.</li><li>2- Extend the period for using an adequate method of contraception after discontinuation of trial treatment.</li><li>3- Clarify the creatine phosphokinase (CPK) criterion for withdrawal of the trial treatment.</li><li>4- Amend the guidance for the monitoring and recording of AEs.</li><li>5- Introduce further guidance on trial treatment modifications and amend the management of specific trial treatment related AEs.</li><li>6- Clarify the assessment of pharmacogenetics (PGx) and biomarkers and to specify informed consent procedures for the collection of PGx samples.</li><li>7- Add an administrative interim analysis.</li><li>8- Clarify instructions for the collection of tumor tissue samples and initial stratification based on histology.</li><li>9- Specify that the corrected QT interval will be calculated using Fredericia's formula.</li><li>10- Clarify the list of prohibited medicines.</li></ol> |
| 14 November 2014 | <p>The purpose of this amendment was to make the following updates:</p> <ol style="list-style-type: none"><li>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.</li><li>2- Introduce the temporary enrollment stop between at least 50 subjects being enrolled and the conclusions derived from the outcome of the futility analysis.</li><li>3- Update the end of trial definition.</li></ol>   |
| 13 March 2015    | <p>The purpose of this amendment was to make the following updates:</p> <ol style="list-style-type: none"><li>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.</li><li>2- Modify the planned trial period (first enrollment-last subject out).</li><li>3- Modify the primary and secondary endpoint analyses.</li><li>4- Modify collection of subject data and endpoint analysis.</li><li>5- Provide information to the Investigator on awareness of dehydration and renal failure secondary to gastrointestinal toxicity.</li></ol>   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported