



Clinical trial results:

A randomized, double-blind, placebo controlled, Phase II/III study of BKM120 plus paclitaxel in patients with HER2 negative inoperable locally advanced or metastatic breast cancer, with or without PI3K pathway activation

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

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2011-005932-24 |
| Trial protocol | AT CZ ES NL GB BE HU IT DE |
| Global end of trial date | 01 June 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 July 2018 |
| First version publication date | 18 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CBKM120F2202 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01572727 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 61324111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 61324111, |

Notes:

Paediatric regulatory details

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

| | |
|--|----|
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
|--|----|

Notes:

Results analysis stage

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

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine whether buparlisib once daily plus weeklypaclitaxel prolongs PFS as per local investigator assessment in patients with HER2- first lineinoperable LABC or MBC patients as compared to placebo plus paclitaxel in either all patients (fullpopulation) or the PI3K pathway activated subpopulation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 16 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 28 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Brazil: 24 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Czech Republic: 6 |
| Country: Number of subjects enrolled | France: 31 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | Hong Kong: 8 |
| Country: Number of subjects enrolled | Hungary: 17 |
| Country: Number of subjects enrolled | Israel: 7 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Japan: 16 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 17 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Russian Federation: 27 |
| Country: Number of subjects enrolled | Singapore: 8 |
| Country: Number of subjects enrolled | Spain: 74 |
| Country: Number of subjects enrolled | Taiwan: 9 |
| Country: Number of subjects enrolled | United States: 82 |
| Worldwide total number of subjects | 416 |
| EEA total number of subjects | 189 |

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) | 336 |
| From 65 to 84 years | 80 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Among 416 randomized patients, 405 patients received the study treatment. Of them, 403 patients had at least one post-baseline safety assessment.

Pre-assignment

Screening details:

A total of approximately 524 patients were to be randomized in a 1:1 ratio to one of the two treatment arms irrespective of the adaptation decision to continue in the full or PI3K pathway activated subpopulation. Randomization was stratified by PI3K activation and Hormone Receptor status.

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 | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | BKM120 and paclitaxel |

Arm description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel was administered once weekly at a dose of 80 mg/m² iv in a 28-day cycle.

| | |
|--|---------------|
| Investigational medicinal product name | burparlisib |
| Investigational medicinal product code | BKM120 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Buparlisib placebo were supplied as 100 mg and 50 mg hard gelatin capsules and was dosed on a flat scale of mg/day.

| | |
|------------------|------------------------|
| Arm title | Placebo and paclitaxel |
|------------------|------------------------|

Arm description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel

| | |
|--|---------------------|
| Arm type | Placebo |
| Investigational medicinal product name | burparlisib placebo |
| Investigational medicinal product code | BKM120 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Buparlisib placebo were supplied as 100 mg and 50 mg hard gelatin capsules and was dosed on a flat scale of mg/day.

| Number of subjects in period 1 | BKM120 and paclitaxel | Placebo and paclitaxel |
|---------------------------------------|------------------------------|-------------------------------|
| Started | 207 | 209 |
| Completed | 0 | 0 |
| Not completed | 207 | 209 |
| Adverse event, serious fatal | 2 | 2 |
| Physician decision | 23 | 9 |
| Adverse event, non-fatal | 43 | 15 |
| Study terminated by sponsor | 61 | 83 |
| Untreated | 4 | 7 |
| Lost to follow-up | 1 | 1 |
| Progressive disease | 59 | 82 |
| Parent/guardian decision | 14 | 9 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|------------------------|
| Reporting group title | BKM120 and paclitaxel |
| Reporting group description: Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel | |
| Reporting group title | Placebo and paclitaxel |
| Reporting group description: Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel | |

| Reporting group values | BKM120 and paclitaxel | Placebo and paclitaxel | Total |
|--|-----------------------|------------------------|-------|
| Number of subjects | 207 | 209 | 416 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 172 | 164 | 336 |
| From 65-84 years | 35 | 45 | 80 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 54.1 | 55.6 | |
| standard deviation | ± 11.13 | ± 10.48 | - |
| Gender, Male/Female Units: Participants | | | |
| Female | 207 | 209 | 416 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|------------------------|
| Reporting group title | BKM120 and paclitaxel |
| Reporting group description: | |
| Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel | |
| Reporting group title | Placebo and paclitaxel |
| Reporting group description: | |
| Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel | |

Primary: Progression-free survival (PFS) assessed by local investigator's assessment

| | |
|--|---|
| End point title | Progression-free survival (PFS) assessed by local investigator's assessment |
| End point description: | |
| PFS was defined as the time from the date of randomization to the date of the event, defined as the first radiologically documented disease progression or death due to any cause. PFS was based on local investigator assessment per RECIST criteria v1.1 | |
| End point type | Primary |
| End point timeframe: | |
| every 8 weeks after randomization Up to 3 months after end of Treatment | |

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168 | 170 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8 (7.2 to 9.2) | 9.2 (7.3 to 11) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis for PFS |
| Comparison groups | Placebo and paclitaxel v BKM120 and paclitaxel |
| Number of subjects included in analysis | 338 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.68 |

Secondary: overall survival by Kaplan-Meier estimate

| | |
|-----------------|---|
| End point title | overall survival by Kaplan-Meier estimate |
|-----------------|---|

End point description:

Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died by the date of analysis cut-off, OS was censored at the date of last contact.

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

End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|----------------------------------|-----------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 207 | 209 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 29.5 (25 to 30) | 9999.9 (-99999.99 to 99999.99) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: overall response rate

| | |
|-----------------|-----------------------|
| End point title | overall response rate |
|-----------------|-----------------------|

End point description:

Percentage of patients with best overall response of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST v1.1

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

End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168 | 170 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 22.6 (16.5 to 29.7) | 27.1 (20.5 to 34.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: duration of response

| | |
|-----------------|----------------------|
| End point title | duration of response |
|-----------------|----------------------|

End point description:

time from the date of the first documented response (CR or PR, which had to be confirmed subsequently) to the date of the first radiologically documented disease progression or death due to disease

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

End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|-----------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | | |
| Units: Months | | | | |
| median (standard deviation) | () | () | | |

Notes:

[1] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

[2] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: time to response

| | |
|-----------------|------------------|
| End point title | time to response |
|-----------------|------------------|

End point description:

time from date of randomization until first documented response (CR or PR, which has to be confirmed subsequently).

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

End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|-----------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | | |
| Units: Months | | | | |
| number (not applicable) | | | | |

Notes:

[3] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: clinical benefit rate (CBR)

| | |
|-----------------|-----------------------------|
| End point title | clinical benefit rate (CBR) |
|-----------------|-----------------------------|

End point description:

CBR was defined as the percentage of patients with an overall response of CR or PR or SD or non-CR/non-PD lasting more than 24 weeks based on local Investigator's assessment according to RECIST v1.1.

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

End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168 | 170 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 26.2 (19.7 to 33.5) | 32.9 (25.9 to 40.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration-time profiles of BKM120 - pharmacokinetics (PK)

| | |
|-----------------|--|
| End point title | Plasma concentration-time profiles of BKM120 - pharmacokinetics (PK) |
|-----------------|--|

End point description:

Summary statistics for PK: plasma concentration-time profiles of BKM120 and appropriate individual PK parameters based on population PK model , if deemed appropriate; each cycle = 28 days

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

End point timeframe:

Cycle 1 day 1, 15, 16, 22 and Cycle 2 day 1.

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|-----------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | | |
| Units: ng*day/mL | | | | |
| median (standard deviation) | () | () | | |

Notes:

[5] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed.

[6] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of ECOG performance status

| | |
|---|---|
| End point title | Time to definitive deterioration of ECOG performance status |
| End point description: | |
| Time to definitive deterioration of the ECOG performance status from baseline | |
| End point type | Secondary |
| End point timeframe: | |
| every 4 weeks | |

| End point values | BKM120 and paclitaxel | Placebo and paclitaxel | | |
|-----------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | | |
| Units: Months | | | | |
| median (standard deviation) | () | () | | |

Notes:

[7] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

[8] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Placebo + Paclitaxel |
|-----------------------|----------------------|

Reporting group description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel

| | |
|-----------------------|-------------------------|
| Reporting group title | Buparlisib + Paclitaxel |
|-----------------------|-------------------------|

Reporting group description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel

| Serious adverse events | Placebo + Paclitaxel | Buparlisib + Paclitaxel | |
|---|----------------------|-------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 42 / 201 (20.90%) | 61 / 202 (30.20%) | |
| number of deaths (all causes) | 5 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| CANCER PAIN | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METASTASES TO CENTRAL NERVOUS SYSTEM | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| DEEP VEIN THROMBOSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 201 (0.50%) | 3 / 202 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENA CAVA THROMBOSIS | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENOUS THROMBOSIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 3 / 202 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FACE OEDEMA | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| LOCALISED OEDEMA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MALaise | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | 7 / 202 (3.47%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| ANAPHYLACTIC REACTION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERSENSITIVITY | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| DIET NONCOMPLIANCE | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| BREAST HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BREAST ULCERATION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (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 | | | |
| ASTHMA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOXIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 6 / 202 (2.97%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Psychiatric disorders | | | |
| ACUTE PSYCHOSIS | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANXIETY | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DELIRIUM | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEPRESSION | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENTAL DISORDER | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PSYCHOTIC DISORDER | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |

| | | | |
|---|-----------------|-----------------|--|
| EJECTION FRACTION DECREASED | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LYMPHOCYTE COUNT INCREASED | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| FALL | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEAD INJURY | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POST-TRAUMATIC PAIN | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXICITY TO VARIOUS AGENTS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| ULNA FRACTURE | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| CARDIO-RESPIRATORY ARREST | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| ALTERED STATE OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRACHIAL PLEXOPATHY | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRAIN COMPRESSION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRAIN OEDEMA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| CEREBRAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ENCEPHALOPATHY | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEMIPARESIS | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METABOLIC ENCEPHALOPATHY | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEIZURE | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL CORD COMPRESSION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| CATARACT | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OPTIC NEUROPATHY | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | 5 / 202 (2.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| NAUSEA | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (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 | | | |
| RASH | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH MACULAR | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH PRURITIC | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| SKIN MASS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN ULCER | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SWELLING FACE | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXIC SKIN ERUPTION | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URTICARIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (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 | | | |
| BACK PAIN | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BONE PAIN | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| 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 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PATHOLOGICAL FRACTURE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (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 | | | |
| ABSCCESS LIMB | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |
| subjects affected / exposed | 5 / 201 (2.49%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| GASTROENTERITIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFUSION SITE INFECTION | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENINGITIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMOCYSTIS JIROVECI INFECTION | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 3 / 202 (1.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STAPHYLOCOCCAL BACTERAEMIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 4 / 202 (1.98%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOGLYCAEMIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo + Paclitaxel | Buparlisib + Paclitaxel | |
|---|----------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 188 / 201 (93.53%) | 196 / 202 (97.03%) | |
| Vascular disorders | | | |
| FLUSHING | | | |
| subjects affected / exposed | 11 / 201 (5.47%) | 7 / 202 (3.47%) | |
| occurrences (all) | 19 | 8 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 10 / 201 (4.98%) | 17 / 202 (8.42%) | |
| occurrences (all) | 13 | 21 | |
| LYMPHOEDEMA | | | |
| subjects affected / exposed | 16 / 201 (7.96%) | 7 / 202 (3.47%) | |
| occurrences (all) | 18 | 8 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 45 / 201 (22.39%) | 48 / 202 (23.76%) | |
| occurrences (all) | 81 | 75 | |
| FATIGUE | | | |
| subjects affected / exposed | 64 / 201 (31.84%) | 67 / 202 (33.17%) | |
| occurrences (all) | 93 | 86 | |
| NON-CARDIAC CHEST PAIN | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 11 / 201 (5.47%) 12 | 4 / 202 (1.98%) 5 | |
| OEDEMA PERIPHERAL subjects affected / exposed occurrences (all) | 50 / 201 (24.88%) 61 | 21 / 202 (10.40%) 25 | |
| PAIN subjects affected / exposed occurrences (all) | 11 / 201 (5.47%) 11 | 9 / 202 (4.46%) 10 | |
| PYREXIA subjects affected / exposed occurrences (all) | 19 / 201 (9.45%) 21 | 29 / 202 (14.36%) 31 | |
| Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) | 28 / 201 (13.93%) 37 | 40 / 202 (19.80%) 46 | |
| DYSPNOEA subjects affected / exposed occurrences (all) | 21 / 201 (10.45%) 24 | 26 / 202 (12.87%) 27 | |
| EPISTAXIS subjects affected / exposed occurrences (all) | 33 / 201 (16.42%) 35 | 29 / 202 (14.36%) 37 | |
| OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all) | 16 / 201 (7.96%) 18 | 12 / 202 (5.94%) 12 | |
| Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) | 31 / 201 (15.42%) 43 | 41 / 202 (20.30%) 47 | |
| DEPRESSION subjects affected / exposed occurrences (all) | 17 / 201 (8.46%) 23 | 50 / 202 (24.75%) 58 | |
| INSOMNIA subjects affected / exposed occurrences (all) | 33 / 201 (16.42%) 36 | 31 / 202 (15.35%) 31 | |
| MOOD ALTERED | | | |

| | | | |
|--|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 201 (2.49%) 7 | 11 / 202 (5.45%) 13 | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 12 / 201 (5.97%) | 35 / 202 (17.33%) | |
| occurrences (all) | 14 | 43 | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 11 / 201 (5.47%) | 30 / 202 (14.85%) | |
| occurrences (all) | 13 | 44 | |
| BLOOD GLUCOSE INCREASED | | | |
| subjects affected / exposed | 10 / 201 (4.98%) | 13 / 202 (6.44%) | |
| occurrences (all) | 16 | 29 | |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 12 / 201 (5.97%) | 7 / 202 (3.47%) | |
| occurrences (all) | 14 | 7 | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 15 / 201 (7.46%) | 15 / 202 (7.43%) | |
| occurrences (all) | 35 | 39 | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 14 / 201 (6.97%) | 30 / 202 (14.85%) | |
| occurrences (all) | 16 | 34 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 14 / 201 (6.97%) | 10 / 202 (4.95%) | |
| occurrences (all) | 43 | 29 | |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 21 / 201 (10.45%) | 33 / 202 (16.34%) | |
| occurrences (all) | 23 | 36 | |
| DYSGEUSIA | | | |
| subjects affected / exposed | 34 / 201 (16.92%) | 39 / 202 (19.31%) | |
| occurrences (all) | 38 | 40 | |
| HEADACHE | | | |
| subjects affected / exposed | 37 / 201 (18.41%) | 35 / 202 (17.33%) | |
| occurrences (all) | 48 | 51 | |

| | | | |
|---|--------------------------|---------------------------|--|
| NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all) | 48 / 201 (23.88%) 69 | 50 / 202 (24.75%) 59 | |
| PARAESTHESIA subjects affected / exposed occurrences (all) | 34 / 201 (16.92%) 46 | 25 / 202 (12.38%) 29 | |
| PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all) | 31 / 201 (15.42%) 39 | 31 / 202 (15.35%) 36 | |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 51 / 201 (25.37%) 78 | 46 / 202 (22.77%) 64 | |
| NEUTROPENIA subjects affected / exposed occurrences (all) | 54 / 201 (26.87%) 147 | 64 / 202 (31.68%) 149 | |
| Eye disorders LACRIMATION INCREASED subjects affected / exposed occurrences (all) | 17 / 201 (8.46%) 18 | 12 / 202 (5.94%) 13 | |
| VISION BLURRED subjects affected / exposed occurrences (all) | 7 / 201 (3.48%) 7 | 19 / 202 (9.41%) 20 | |
| Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all) | 22 / 201 (10.95%) 26 | 27 / 202 (13.37%) 32 | |
| ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) | 14 / 201 (6.97%) 16 | 11 / 202 (5.45%) 12 | |
| CONSTIPATION subjects affected / exposed occurrences (all) | 38 / 201 (18.91%) 55 | 47 / 202 (23.27%) 58 | |
| DIARRHOEA subjects affected / exposed occurrences (all) | 68 / 201 (33.83%) 123 | 109 / 202 (53.96%) 191 | |
| DRY MOUTH | | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed | 10 / 201 (4.98%) | 12 / 202 (5.94%) | |
| occurrences (all) | 11 | 12 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 15 / 201 (7.46%) | 23 / 202 (11.39%) | |
| occurrences (all) | 18 | 26 | |
| NAUSEA | | | |
| subjects affected / exposed | 51 / 201 (25.37%) | 83 / 202 (41.09%) | |
| occurrences (all) | 72 | 126 | |
| STOMATITIS | | | |
| subjects affected / exposed | 24 / 201 (11.94%) | 56 / 202 (27.72%) | |
| occurrences (all) | 31 | 77 | |
| VOMITING | | | |
| subjects affected / exposed | 30 / 201 (14.93%) | 39 / 202 (19.31%) | |
| occurrences (all) | 52 | 67 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 104 / 201 (51.74%) | 103 / 202 (50.99%) | |
| occurrences (all) | 105 | 106 | |
| DRY SKIN | | | |
| subjects affected / exposed | 13 / 201 (6.47%) | 28 / 202 (13.86%) | |
| occurrences (all) | 15 | 35 | |
| ERYTHEMA | | | |
| subjects affected / exposed | 17 / 201 (8.46%) | 11 / 202 (5.45%) | |
| occurrences (all) | 19 | 13 | |
| NAIL DISCOLOURATION | | | |
| subjects affected / exposed | 14 / 201 (6.97%) | 7 / 202 (3.47%) | |
| occurrences (all) | 14 | 7 | |
| NAIL DISORDER | | | |
| subjects affected / exposed | 19 / 201 (9.45%) | 7 / 202 (3.47%) | |
| occurrences (all) | 20 | 8 | |
| ONYCHOMADESIS | | | |
| subjects affected / exposed | 11 / 201 (5.47%) | 7 / 202 (3.47%) | |
| occurrences (all) | 11 | 8 | |
| PRURITUS | | | |
| subjects affected / exposed | 30 / 201 (14.93%) | 32 / 202 (15.84%) | |
| occurrences (all) | 35 | 42 | |

| | | | |
|---|-------------------|-------------------|--|
| RASH | | | |
| subjects affected / exposed | 43 / 201 (21.39%) | 86 / 202 (42.57%) | |
| occurrences (all) | 62 | 111 | |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 8 / 201 (3.98%) | 12 / 202 (5.94%) | |
| occurrences (all) | 13 | 19 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 32 / 201 (15.92%) | 23 / 202 (11.39%) | |
| occurrences (all) | 37 | 26 | |
| BACK PAIN | | | |
| subjects affected / exposed | 22 / 201 (10.95%) | 21 / 202 (10.40%) | |
| occurrences (all) | 25 | 24 | |
| BONE PAIN | | | |
| subjects affected / exposed | 14 / 201 (6.97%) | 10 / 202 (4.95%) | |
| occurrences (all) | 17 | 14 | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 12 / 201 (5.97%) | 8 / 202 (3.96%) | |
| occurrences (all) | 13 | 9 | |
| MYALGIA | | | |
| subjects affected / exposed | 27 / 201 (13.43%) | 22 / 202 (10.89%) | |
| occurrences (all) | 35 | 35 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 40 / 201 (19.90%) | 27 / 202 (13.37%) | |
| occurrences (all) | 51 | 37 | |
| Infections and infestations | | | |
| RHINITIS | | | |
| subjects affected / exposed | 9 / 201 (4.48%) | 11 / 202 (5.45%) | |
| occurrences (all) | 10 | 11 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 23 / 201 (11.44%) | 11 / 202 (5.45%) | |
| occurrences (all) | 31 | 12 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 18 / 201 (8.96%) | 18 / 202 (8.91%) | |
| occurrences (all) | 25 | 21 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|-------------------|-------------------|--|
| DECREASED APPETITE | | | |
| subjects affected / exposed | 26 / 201 (12.94%) | 64 / 202 (31.68%) | |
| occurrences (all) | 32 | 71 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 22 / 201 (10.95%) | 82 / 202 (40.59%) | |
| occurrences (all) | 58 | 156 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 6 / 201 (2.99%) | 19 / 202 (9.41%) | |
| occurrences (all) | 7 | 34 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 31 July 2012 | The purpose of this protocol amendment was to add contraceptive guidance in alignment with the local summary of product characteristics for contraception recommendations after discontinuation of paclitaxel study drug. |
| 26 May 2013 | The main purpose of this protocol amendment was to update and align the management of selected AEs across the buparlisib program, specifically psychiatric disorders, hyperglycemia, stomatitis and skin rash, and to increase the permitted treatment interruption period for buparlisib/placebo from 21 to 28 days. Moreover, due to the very low frequency of PI3KCA mutations in exon5 and PTEN mutations overall in breast cancer, the definition of the PI3K pathway activation status (one of the two stratification factors) was modified and no longer included the above mentioned mutations. |
| 13 September 2013 | The main purpose of this protocol amendment was to convert the existing Phase II trial into a Phase II/III study by implementing an adaptive Phase II/III seamless design with a Bayesian decision tool for targeted therapy in oncology as described by Brannath W, Zuber E, Branson M, et al. (2009), in accordance with the published FDA guidelines on adaptive designs and enrichment strategies (FDA Guidance 2010 and 2012), and the EU 2007 reflection paper (CHMP/EWP/2459/02). Prior to implementation, scientific advice was sought and the planned amendment discussed with the FDA, EMA and PMDA |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The safety set included all randomized patients who received at least one dose of the study treatment (either buparlisib + paclitaxel or matching placebo + paclitaxel) and had at least one post-baseline safety assessment.

Notes: