



Clinical trial results:

A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-006087-49 |
| Trial protocol | SE DE ES GB NL GR IT |
| Global end of trial date | 28 February 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 (current) |
| This version publication date | 09 April 2021 |
| First version publication date | 14 March 2020 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 115306 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01584648 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Novartis Pharma AG, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Novartis Pharma AG, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 28 February 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective was to establish the superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib placebo (dabrafenib monotherapy) with respect to progression free survival (PFS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

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 | 04 May 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 2 |
| Country: Number of subjects enrolled | Australia: 40 |
| Country: Number of subjects enrolled | Canada: 14 |
| Country: Number of subjects enrolled | France: 41 |
| Country: Number of subjects enrolled | Germany: 86 |
| Country: Number of subjects enrolled | Greece: 21 |
| Country: Number of subjects enrolled | Italy: 49 |
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Russian Federation: 45 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | Sweden: 18 |
| Country: Number of subjects enrolled | Ukraine: 22 |
| Country: Number of subjects enrolled | United Kingdom: 33 |
| Country: Number of subjects enrolled | United States: 23 |
| Worldwide total number of subjects | 423 |
| EEA total number of subjects | 244 |

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) | 305 |
| From 65 to 84 years | 115 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 103 centers in 14 countries worldwide: Argentina (1), Australia (6), Canada (5), France (8), Germany (25), Greece (3), Italy (8), Netherlands (3), Russia (4), Spain (7), Sweden (4), Ukraine (7), United Kingdom (10), and USA (12).

Pre-assignment

Screening details:

Approximately, 340 subjects were planned to be randomized in a 1:1 ratio (170 subjects each in combination therapy and monotherapy). A total of 423 subjects with unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma were randomized to dabrafenib and trametinib (n=211) or dabrafenib and placebo (n=212).

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dabrafenib + Trametinib |

Arm description:

Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dabrafenib |
| Investigational medicinal product code | |
| Other name | GSK2118436 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Dabrafenib 150 mg twice daily

| | |
|--|------------|
| Investigational medicinal product name | Trametinib |
| Investigational medicinal product code | |
| Other name | GSK1120212 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Trametinib 2 mg once daily

| | |
|------------------|----------------------|
| Arm title | Dabrafenib + Placebo |
|------------------|----------------------|

Arm description:

Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Dabrafenib |
| Investigational medicinal product code | |
| Other name | GSK2118436 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dabrafenib 150 mg twice daily | |
| Investigational medicinal product name | Trametinib placebo |
| Investigational medicinal product code | |
| Other name | Placebo |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dabrafenib 150 mg twice daily and trametinib placebo | |

| Number of subjects in period 1 | Dabrafenib + Trametinib | Dabrafenib + Placebo |
|---|------------------------------------|---------------------------------|
| Started | 211 | 212 |
| Safety Set | 209 | 211 |
| Crossover Population | 0 | 28 |
| Completed | 0 | 0 |
| Not completed | 211 | 212 |
| Adverse event, serious fatal | 136 | 146 |
| Study closed/terminated | 50 | 23 |
| Crossover to Dabrafenib + Trametinib | - | 28 |
| Lost to follow-up | 9 | 9 |
| Investigator discretion | 3 | 2 |
| Withdrew consent | 13 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dabrafenib + Trametinib |
|-----------------------|-------------------------|

Reporting group description:

Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.

| | |
|-----------------------|----------------------|
| Reporting group title | Dabrafenib + Placebo |
|-----------------------|----------------------|

Reporting group description:

Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.

| Reporting group values | Dabrafenib + Trametinib | Dabrafenib + Placebo | Total |
|--|-------------------------|----------------------|-------|
| Number of subjects | 211 | 212 | 423 |
| 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) | 154 | 151 | 305 |
| From 65-84 years | 55 | 60 | 115 |
| 85 years and over | 2 | 1 | 3 |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 100 | 98 | 198 |
| Male | 111 | 114 | 225 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| African American/African Heritage | 0 | 1 | 1 |
| White - White/Caucasian/European Heritage | 211 | 211 | 422 |
| AgeContinuous | | | |
| Units: Years | | | |
| arithmetic mean | 55.1 | 55.3 | |
| standard deviation | ± 13.33 | ± 13.75 | - |

End points

End points reporting groups

| | |
|--|-----------------------------------|
| Reporting group title | Dabrafenib + Trametinib |
| Reporting group description: Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. | |
| Reporting group title | Dabrafenib + Placebo |
| Reporting group description: Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis. | |
| Subject analysis set title | Crossover Dabrafenib + Trametinib |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Crossover Dabrafenib + Trametinib | |

Primary: Progression-Free Survival (PFS) as assessed by the investigator

| | |
|--|---|
| End point title | Progression-Free Survival (PFS) as assessed by the investigator |
| End point description: PFS is defined as the interval between the date of randomization and the earliest date of PD or death due to any cause. PD was based on radiographic or photographic evidence, and assessments were made by the investigator according to RECIST, version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. The appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation, was also included as PD. Participants who received anti-cancer therapy prior to the date of documented events, were censored at the last adequate assessment prior to the initiation of therapy. If the participant did not have documented progression or death, PFS was censored at the date of the last adequate assessment. | |
| End point type | Primary |
| End point timeframe: From randomization until the earliest date of disease progression (PD) or death due to any cause (up to approximately 6 years) | |

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 211 | 212 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.2 (8.1 to 12.8) | 8.8 (5.9 to 9.3) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Progression-Free Survival (PFS) |
| Comparison groups | Dabrafenib + Trametinib v Dabrafenib + Placebo |
| Number of subjects included in analysis | 423 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.91 |

Secondary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS is defined as the interval of time between the date of randomization and the date of death due to any cause. For the participants who did not die, overall survival was censored at the date of last contact. | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization until date of death due to any cause (up to approximately 6 years) | |

| | | | | |
|----------------------------------|-------------------------|----------------------|--|--|
| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 211 | 212 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 25.8 (19.2 to 38.2) | 18.7 (15.2 to 23.1) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Overall Survival (OS) |
| Comparison groups | Dabrafenib + Trametinib v Dabrafenib + Placebo |
| Number of subjects included in analysis | 423 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.02 |

Secondary: Objective Response Rate (ORR) as assessed by the investigator

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) as assessed by the investigator |
|-----------------|---|

End point description:

ORR is defined as the percentage of participants with a confirmed complete response (CR) or partial response (PR). A participant was defined as a responder if he/she sustained a complete response (CR: the disappearance of all target lesions and any pathological lymph nodes must have a short axis of <10 mm and the disappearance of all non-target lesions) or partial response (PR: at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters or the persistence of 1 or more non-target lesions or lymph nodes identified as a site of disease at Baseline with a short axis of ≥ 10 mm). Only descriptive analysis performed.

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

End point timeframe:

From randomization until the first documented complete response or partial response (up to approximately 6 years)

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | | |
|-----------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 210 | 210 | | |
| Units: Participants | 146 | 113 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

| | |
|-----------------|----------------------------|
| End point title | Duration of Response (DoR) |
|-----------------|----------------------------|

End point description:

Duration of response is defined as the time from the first documented complete response (CR: the disappearance of all target lesions and any pathological lymph nodes must have a short axis of <10 mm and the disappearance of all non-target lesions) or partial response (PR: at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters or the persistence of 1 or more non-target lesions or lymph nodes identified as a site of disease at Baseline with a short axis of ≥ 10 mm) until disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5mm or the appearance of one or more new lesions, or the worsening of non target lesions significant enough to require study treatment discontinuation. PD was based on the radiological evidence by investigator. Only descriptive analysis performed.

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

End point timeframe:

From the time of the first documented response (CR or PR) until disease progression (up to approximately 6 years)

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 146 | 114 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.9 (9.3 to 18.4) | 10.2 (8.3 to 13.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events and Serious Adverse Events

| | |
|-----------------|---|
| End point title | Number of Participants with Adverse Events and Serious Adverse Events |
|-----------------|---|

End point description:

Analysis of absolute and relative frequencies for Adverse Event (AE) and Serious Adverse Event (SAE) by primary System Organ Class (SOC) to characterize the safety of dabrafenib and trametinib combination therapy through the monitoring of relevant clinical and laboratory safety parameters. In addition, new malignancies and AEs possibly related to study treatment were collected even if they occurred more than 30 days post-treatment. Only descriptive analysis performed.

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

End point timeframe:

From the time the first dose of study treatment administered until 30 days after discontinuation of study treatment (up to approximately 6 years).

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | Crossover Dabrafenib + Trametinib | |
|------------------------------|-------------------------|----------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 209 | 211 | 28 | |
| Units: Participants | | | | |
| Adverse Event (AEs) | 203 | 205 | 24 | |
| Serious Adverse Event (SAEs) | 100 | 80 | 8 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Trametinib Pharmacokinetic Concentrations

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|-----------------|---|
| End point title | Trametinib Pharmacokinetic Concentrations |
|-----------------|---|

End point description:

Blood samples were collected for Pharmacokinetic (PK) analysis in all participants. Three blood samples were collected at Week 8: pre-dose, 1-3 hours post dose, and 4-6 hours post dose. One pre-dose blood sample was obtained at Weeks 16 and 24. Only descriptive analysis performed.

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

End point timeframe:

Week 8 (0, 1-3, 4-6 hours post dose), Weeks 16 and 24 (0 hour pre-dose)

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | | |
|--|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 194 | | |
| Units: Nanogram per Milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8, pre-dose | 9.9209 (± 3.86587) | 0.0000 (± 0.00000) | | |
| Week 8, 1-3 hours | 19.0382 (± 6.86542) | 0.0261 (± 0.34598) | | |
| Week 8, 4-6 hours | 16.7496 (± 5.64363) | 0.0000 (± 0.00000) | | |
| Week 16 pre-dose | 11.0385 (± 4.79185) | 0.0039 (± 0.03548) | | |
| Week 24 pre-dose | 11.5167 (± 5.19171) | 0.0548 (± 0.62447) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dabrafenib and Dabrafenib Metabolites (Hydroxy-, Carboxy- and Desmethyl-Dabrafenib) Concentrations

| | |
|-----------------|--|
| End point title | Dabrafenib and Dabrafenib Metabolites (Hydroxy-, Carboxy- and Desmethyl-Dabrafenib) Concentrations |
|-----------------|--|

End point description:

Blood samples were collected for PK analysis in all participants. Three blood samples were collected at Week 8: pre-dose, 1-3 hours post dose, and 4-6 hours post dose. One pre-dose blood sample was obtained at Weeks 16 and 24. Plasma concentrations of Dabrafenib (GSK2118436) and its metabolites (Hydroxy-Dabrafenib (GSK2285403), Carboxy-Dabrafenib (GSK2298683), and Desmethyl-Dabrafenib (GSK2167542)) were determined using the currently approved analytical methodology. Only descriptive analysis performed.

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

End point timeframe:

Week 8 (0, 1-3, 4-6 hours post dose), Weeks 16 and 24 (0 hour pre-dose)

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | | |
|--|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 194 | | |
| Units: Nanogram per Milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| GSK2118436, Week 8, pre-dose | 92.1 (± 204.85) | 64.4 (± 96.98) | | |

| | | | | |
|-------------------------------|--------------------|--------------------|--|--|
| GSK2118436, Week 8, 1-3 hours | 1309.6 (± 982.25) | 1362.3 (± 992.97) | | |
| GSK2118436, Week 8, 4-6 hours | 458.9 (± 318.59) | 539.7 (± 553.09) | | |
| GSK2118436, Week 16 pre-dose | 151.6 (± 261.31) | 151.02 (± 381.32) | | |
| GSK2118436, Week 24 pre-dose | 167.0 (± 346.97) | 156.5 (± 357.50) | | |
| GSK2285403, Week 8, pre-dose | 346.6 (± 261.73) | 308.9 (± 224.56) | | |
| GSK2285403, Week 8, 1-3 hours | 361.7 (± 245.92) | 341.8 (± 240.96) | | |
| GSK2285403, Week 8, 4-6 hours | 316.9 (± 208.51) | 328.1 (± 234.95) | | |
| GSK2285403, Week 16 pre-dose | 335.0 (± 228.26) | 331.0 (± 250.04) | | |
| GSK2285403, Week 24 pre-dose | 306.2 (± 203.77) | 312.8 (± 250.28) | | |
| GSK2298683, Week 8, pre-dose | 82.0 (± 123.93) | 76.7 (± 109.09) | | |
| GSK2298683, Week 8, 1-3 hours | 648.5 (± 459.01) | 672.7 (± 519.45) | | |
| GSK2298683, Week 8, 4-6 hours | 391.3 (± 206.70) | 502.2 (± 356.72) | | |
| GSK2298683, Week 16 pre-dose | 128.7 (± 174.26) | 121.1 (± 195.15) | | |
| GSK2298683, Week 24 pre-dose | 126.1 (± 219.82) | 145.7 (± 265.57) | | |
| GSK2167542, Week 8, pre-dose | 3237.2 (± 1694.66) | 3469.4 (± 1854.02) | | |
| GSK2167542, Week 8, 1-3 hours | 4286.3 (± 2514.50) | 4456.6 (± 2687.32) | | |
| GSK2167542, Week 8, 4-6 hours | 6238.3 (± 2716.05) | 6891.6 (± 2739.07) | | |
| GSK2167542, Week 16 pre-dose | 3842.4 (± 2428.74) | 4114.1 (± 2432.72) | | |
| GSK2167542, Week 24 pre-dose | 3617.9 (± 2645.51) | 4193.2 (± 2730.78) | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

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|-----------------|----------------------|
| End point title | All collected deaths |
|-----------------|----------------------|

End point description:

Pre-treatment deaths were collected from screening visit up to the first day of treatment, for a maximum duration of 28 days. Patients who died during the screening period are considered as screen failure.

On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 77.4 months (treatment duration ranged from 0.1 to 76.4 months).

Deaths post treatment survival follow up were collected after the on- treatment period, up to approximately 6 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

up to 28 days before Day 1 (Screening), up to 77.4 months (on-treatment), up to approximately 6 years (study duration)

| End point values | Dabrafenib + Trametinib | Dabrafenib + Placebo | Crossover Dabrafenib + Trametinib | |
|-----------------------------|----------------------------|-------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 210 | 211 | 28 | |
| Units: Participants | | | | |
| Pre-treatment deaths | 1 | 0 | 0 | |
| On-treatment deaths | 29 | 25 | 0 | |
| Post-treatment deaths | 106 | 121 | 5 | |
| All deaths | 136 | 146 | 5 | |

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 are reported in this record from 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 | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dabrafenib + Trametinib |
|-----------------------|-------------------------|

Reporting group description:

Dabrafenib + Trametinib

| | |
|-----------------------|----------------------|
| Reporting group title | Dabrafenib + Placebo |
|-----------------------|----------------------|

Reporting group description:

Dabrafenib + Placebo

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Crossover Dabrafenib + Trametinib |
|-----------------------|-----------------------------------|

Reporting group description:

Crossover Dabrafenib + Trametinib

| | |
|-----------------------|--------------|
| Reporting group title | All Patients |
|-----------------------|--------------|

Reporting group description:

All Patients

| Serious adverse events | Dabrafenib + Trametinib | Dabrafenib + Placebo | Crossover Dabrafenib + Trametinib |
|---|-------------------------|----------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 100 / 209 (47.85%) | 80 / 211 (37.91%) | 8 / 28 (28.57%) |
| number of deaths (all causes) | 135 | 146 | 5 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |

| | | | |
|---|-----------------|------------------|----------------|
| subjects affected / exposed | 8 / 209 (3.83%) | 14 / 211 (6.64%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 11 / 13 | 13 / 18 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct adenocarcinoma | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Bowen's disease | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 2 / 211 (0.95%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hodgkin's disease | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Keratoacanthoma | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipofibroma | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |

| | | | |
|--|-----------------|------------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteosarcoma | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phaeochromocytoma | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Schwannoma | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 7 / 211 (3.32%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 3 / 3 | 7 / 8 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 15 / 211 (7.11%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 4 / 4 | 15 / 17 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 2 / 211 (0.95%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 3 / 7 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis superficial | | | |

| | | | |
|--|------------------|-----------------|----------------|
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |
| subjects affected / exposed | 10 / 209 (4.78%) | 3 / 211 (1.42%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 12 / 12 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drowning | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|-------------------|------------------|----------------|
| subjects affected / exposed | 36 / 209 (17.22%) | 15 / 211 (7.11%) | 2 / 28 (7.14%) |
| occurrences causally related to treatment / all | 59 / 59 | 16 / 17 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory depression | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mania | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Organic brain syndrome | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase | | | |

| | | | |
|---|------------------|-----------------|----------------|
| increased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 13 / 209 (6.22%) | 5 / 211 (2.37%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 12 / 17 | 5 / 5 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal function test abnormal | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural persistent drain fluid | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 2 / 211 (0.95%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central nervous system lesion | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 4 / 209 (1.91%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 209 (2.39%) | 3 / 211 (1.42%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemolytic uraemic syndrome | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iridocyclitis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uveitis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 209 (1.91%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute abdomen | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jejunal perforation | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritoneal haemorrhage | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 209 (1.44%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic haematoma | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatosis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin lesion | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephritis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvi-ureteric obstruction | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercreatinaemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immunoglobulin G4 related disease | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc degeneration | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Kidney infection | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 209 (0.48%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superinfection | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 2 / 211 (0.95%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | All Patients | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 183 / 420 (43.57%) | | |
| number of deaths (all causes) | 286 | | |
| number of deaths resulting from adverse events | 1 | | |

| | | | |
|---|------------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 22 / 420 (5.24%) | | |
| occurrences causally related to treatment / all | 24 / 31 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bile duct adenocarcinoma | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Bowen's disease | | | |
| subjects affected / exposed | 5 / 420 (1.19%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hodgkin's disease | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Keratoacanthoma | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| Lipofibroma | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant melanoma | | | | |
| subjects affected / exposed | 3 / 420 (0.71%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteosarcoma | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Papillary thyroid cancer | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Phaeochromocytoma | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate cancer | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Schwannoma | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma | | | | |
| subjects affected / exposed | 11 / 420 (2.62%) | | | |
| occurrences causally related to treatment / all | 10 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma of skin | | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 18 / 420 (4.29%) | | |
| occurrences causally related to treatment / all | 19 / 22 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 9 / 420 (2.14%) | | |
| occurrences causally related to treatment / all | 4 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chills | | | |
| subjects affected / exposed | 13 / 420 (3.10%) | | |
| occurrences causally related to treatment / all | 16 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drowning | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 420 (0.95%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 420 (0.71%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 51 / 420 (12.14%) | | |
| occurrences causally related to treatment / all | 77 / 78 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 420 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory depression | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 4 / 420 (0.95%) | | |
| occurrences causally related to treatment / all | 5 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mania | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Organic brain syndrome | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |

| | | | | |
|---|------------------|--|--|--|
| Alanine aminotransferase increased | | | | |
| subjects affected / exposed | 4 / 420 (0.95%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood alkaline phosphatase increased | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ejection fraction decreased | | | | |
| subjects affected / exposed | 19 / 420 (4.52%) | | | |
| occurrences causally related to treatment / all | 18 / 23 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Forced expiratory volume decreased | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoglobin decreased | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic enzyme increased | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutrophil count decreased | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oxygen saturation decreased | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal function test abnormal | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meniscus injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural persistent drain fluid | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 420 (1.19%) | | |
| occurrences causally related to treatment / all | 4 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 420 (0.71%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiovascular insufficiency | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain oedema | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Central nervous system lesion | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cerebral infarction | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epilepsy | | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Facial paralysis | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hemiplegia | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorder | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paraesthesia | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Presyncope | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 5 / 420 (1.19%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 420 (1.90%) | | |
| occurrences causally related to treatment / all | 1 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemolytic uraemic syndrome | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypochromic anaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iridocyclitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uveitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Abdominal pain | | | | |
| subjects affected / exposed | 6 / 420 (1.43%) | | | |
| occurrences causally related to treatment / all | 2 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain upper | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute abdomen | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorder | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrooesophageal reflux disease | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal perforation | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Jejunal perforation | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis acute | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritoneal haemorrhage | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal haemorrhage | | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper gastrointestinal haemorrhage | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 420 (0.71%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic haematoma | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatosis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkeratosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephritis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvi-ureteric obstruction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Compartment syndrome | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercreatinaemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immunoglobulin G4 related disease | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 420 (0.71%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile infection | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Kidney infection | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngitis | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenic sepsis | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 8 / 420 (1.90%) | | | |
| occurrences causally related to treatment / all | 1 / 8 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pseudomonas infection | | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superinfection | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 420 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 420 (0.95%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 420 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 420 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Dabrafenib + Trametinib | Dabrafenib + Placebo | Crossover Dabrafenib + Trametinib |
|---|------------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 194 / 209 (92.82%) | 200 / 211 (94.79%) | 23 / 28 (82.14%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 16 / 211 (7.58%) | 0 / 28 (0.00%) |
| occurrences (all) | 3 | 20 | 0 |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 22 / 211 (10.43%) | 0 / 28 (0.00%) |
| occurrences (all) | 13 | 31 | 0 |
| Skin papilloma | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 46 / 211 (21.80%) | 1 / 28 (3.57%) |
| occurrences (all) | 9 | 81 | 1 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 8 / 209 (3.83%) | 5 / 211 (2.37%) | 2 / 28 (7.14%) |
| occurrences (all) | 9 | 5 | 2 |
| Hypertension | | | |
| subjects affected / exposed | 51 / 209 (24.40%) | 33 / 211 (15.64%) | 2 / 28 (7.14%) |
| occurrences (all) | 76 | 42 | 4 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 29 / 209 (13.88%) | 30 / 211 (14.22%) | 4 / 28 (14.29%) |
| occurrences (all) | 45 | 38 | 9 |
| Chest pain | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 5 / 211 (2.37%) | 0 / 28 (0.00%) |
| occurrences (all) | 14 | 6 | 0 |
| Chills | | | |
| subjects affected / exposed | 63 / 209 (30.14%) | 34 / 211 (16.11%) | 3 / 28 (10.71%) |
| occurrences (all) | 218 | 59 | 7 |
| Fatigue | | | |
| subjects affected / exposed | 79 / 209 (37.80%) | 79 / 211 (37.44%) | 7 / 28 (25.00%) |
| occurrences (all) | 107 | 99 | 7 |

| | | | |
|--|---------------------------|--------------------------|------------------------|
| Influenza like illness subjects affected / exposed occurrences (all) | 17 / 209 (8.13%) 58 | 12 / 211 (5.69%) 17 | 3 / 28 (10.71%) 21 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 48 / 209 (22.97%) 72 | 17 / 211 (8.06%) 19 | 2 / 28 (7.14%) 2 |
| Pain subjects affected / exposed occurrences (all) | 14 / 209 (6.70%) 14 | 9 / 211 (4.27%) 9 | 1 / 28 (3.57%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 118 / 209 (56.46%) 441 | 63 / 211 (29.86%) 111 | 10 / 28 (35.71%) 47 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 209 (0.48%) 1 | 2 / 211 (0.95%) 2 | 2 / 28 (7.14%) 2 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 51 / 209 (24.40%) 73 | 46 / 211 (21.80%) 63 | 3 / 28 (10.71%) 8 |
| Dyspnoea subjects affected / exposed occurrences (all) | 16 / 209 (7.66%) 21 | 19 / 211 (9.00%) 20 | 1 / 28 (3.57%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 21 / 209 (10.05%) 44 | 11 / 211 (5.21%) 15 | 1 / 28 (3.57%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 24 / 209 (11.48%) 31 | 11 / 211 (5.21%) 20 | 0 / 28 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 12 / 209 (5.74%) 12 | 6 / 211 (2.84%) 7 | 3 / 28 (10.71%) 3 |
| Depression subjects affected / exposed occurrences (all) | 9 / 209 (4.31%) 9 | 12 / 211 (5.69%) 12 | 1 / 28 (3.57%) 1 |

| | | | |
|--|-------------------|------------------|-----------------|
| Insomnia | | | |
| subjects affected / exposed | 11 / 209 (5.26%) | 18 / 211 (8.53%) | 1 / 28 (3.57%) |
| occurrences (all) | 15 | 21 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 25 / 209 (11.96%) | 12 / 211 (5.69%) | 1 / 28 (3.57%) |
| occurrences (all) | 31 | 13 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 29 / 209 (13.88%) | 8 / 211 (3.79%) | 0 / 28 (0.00%) |
| occurrences (all) | 36 | 8 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 18 / 209 (8.61%) | 8 / 211 (3.79%) | 3 / 28 (10.71%) |
| occurrences (all) | 19 | 11 | 4 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 8 / 209 (3.83%) | 0 / 211 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 10 | 0 | 3 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 8 / 209 (3.83%) | 2 / 211 (0.95%) | 2 / 28 (7.14%) |
| occurrences (all) | 9 | 4 | 2 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 8 / 209 (3.83%) | 2 / 211 (0.95%) | 2 / 28 (7.14%) |
| occurrences (all) | 11 | 2 | 2 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 7 / 209 (3.35%) | 2 / 211 (0.95%) | 3 / 28 (10.71%) |
| occurrences (all) | 7 | 2 | 3 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 5 / 211 (2.37%) | 4 / 28 (14.29%) |
| occurrences (all) | 6 | 6 | 4 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 7 / 209 (3.35%) | 0 / 211 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 8 | 0 | 7 |
| Weight decreased | | | |
| subjects affected / exposed | 13 / 209 (6.22%) | 19 / 211 (9.00%) | 0 / 28 (0.00%) |
| occurrences (all) | 15 | 19 | 0 |

| | | | |
|--|-------------------|-------------------|-----------------|
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 2 / 211 (0.95%) | 2 / 28 (7.14%) |
| occurrences (all) | 9 | 2 | 3 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 2 / 28 (7.14%) |
| occurrences (all) | 0 | 1 | 2 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 209 (0.96%) | 2 / 211 (0.95%) | 2 / 28 (7.14%) |
| occurrences (all) | 2 | 2 | 2 |
| Tachycardia | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 13 / 211 (6.16%) | 3 / 28 (10.71%) |
| occurrences (all) | 8 | 13 | 3 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 32 / 209 (15.31%) | 15 / 211 (7.11%) | 1 / 28 (3.57%) |
| occurrences (all) | 42 | 24 | 3 |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 209 (2.87%) | 13 / 211 (6.16%) | 2 / 28 (7.14%) |
| occurrences (all) | 7 | 14 | 2 |
| Headache | | | |
| subjects affected / exposed | 71 / 209 (33.97%) | 63 / 211 (29.86%) | 6 / 28 (21.43%) |
| occurrences (all) | 165 | 128 | 9 |
| Paraesthesia | | | |
| subjects affected / exposed | 9 / 209 (4.31%) | 12 / 211 (5.69%) | 1 / 28 (3.57%) |
| occurrences (all) | 9 | 13 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 16 / 209 (7.66%) | 22 / 211 (10.43%) | 3 / 28 (10.71%) |
| occurrences (all) | 21 | 23 | 3 |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 209 (3.35%) | 1 / 211 (0.47%) | 2 / 28 (7.14%) |
| occurrences (all) | 7 | 1 | 3 |
| Neutropenia | | | |

| | | | |
|--|--------------------------|-------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 20 / 209 (9.57%) 26 | 5 / 211 (2.37%) 5 | 3 / 28 (10.71%) 6 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 9 / 209 (4.31%) 9 | 2 / 211 (0.95%) 2 | 2 / 28 (7.14%) 2 |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 5 / 209 (2.39%) 5 | 2 / 211 (0.95%) 2 | 3 / 28 (10.71%) 3 |
| Eye disorders Blepharitis subjects affected / exposed occurrences (all) | 2 / 209 (0.96%) 2 | 0 / 211 (0.00%) 0 | 2 / 28 (7.14%) 2 |
| Cataract subjects affected / exposed occurrences (all) | 2 / 209 (0.96%) 3 | 4 / 211 (1.90%) 5 | 3 / 28 (10.71%) 4 |
| Dry eye subjects affected / exposed occurrences (all) | 11 / 209 (5.26%) 15 | 4 / 211 (1.90%) 6 | 1 / 28 (3.57%) 1 |
| Vision blurred subjects affected / exposed occurrences (all) | 10 / 209 (4.78%) 10 | 5 / 211 (2.37%) 7 | 3 / 28 (10.71%) 3 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 29 / 209 (13.88%) 57 | 17 / 211 (8.06%) 22 | 1 / 28 (3.57%) 3 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 20 / 209 (9.57%) 29 | 12 / 211 (5.69%) 13 | 3 / 28 (10.71%) 4 |
| Constipation subjects affected / exposed occurrences (all) | 27 / 209 (12.92%) 33 | 22 / 211 (10.43%) 25 | 3 / 28 (10.71%) 7 |
| Diarrhoea subjects affected / exposed occurrences (all) | 67 / 209 (32.06%) 149 | 34 / 211 (16.11%) 53 | 9 / 28 (32.14%) 12 |
| Dry mouth | | | |

| | | | |
|--|-------------------|-------------------|-----------------|
| subjects affected / exposed | 18 / 209 (8.61%) | 6 / 211 (2.84%) | 1 / 28 (3.57%) |
| occurrences (all) | 18 | 7 | 1 |
| Nausea | | | |
| subjects affected / exposed | 79 / 209 (37.80%) | 57 / 211 (27.01%) | 7 / 28 (25.00%) |
| occurrences (all) | 175 | 89 | 11 |
| Vomiting | | | |
| subjects affected / exposed | 57 / 209 (27.27%) | 31 / 211 (14.69%) | 3 / 28 (10.71%) |
| occurrences (all) | 134 | 48 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 15 / 211 (7.11%) | 1 / 28 (3.57%) |
| occurrences (all) | 35 | 23 | 1 |
| Alopecia | | | |
| subjects affected / exposed | 19 / 209 (9.09%) | 61 / 211 (28.91%) | 0 / 28 (0.00%) |
| occurrences (all) | 20 | 64 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 21 / 209 (10.05%) | 8 / 211 (3.79%) | 0 / 28 (0.00%) |
| occurrences (all) | 25 | 9 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 30 / 209 (14.35%) | 33 / 211 (15.64%) | 3 / 28 (10.71%) |
| occurrences (all) | 36 | 37 | 3 |
| Eczema | | | |
| subjects affected / exposed | 19 / 209 (9.09%) | 8 / 211 (3.79%) | 2 / 28 (7.14%) |
| occurrences (all) | 23 | 8 | 2 |
| Erythema | | | |
| subjects affected / exposed | 24 / 209 (11.48%) | 16 / 211 (7.58%) | 1 / 28 (3.57%) |
| occurrences (all) | 31 | 17 | 1 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 209 (0.00%) | 18 / 211 (8.53%) | 0 / 28 (0.00%) |
| occurrences (all) | 0 | 18 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 14 / 209 (6.70%) | 9 / 211 (4.27%) | 1 / 28 (3.57%) |
| occurrences (all) | 43 | 11 | 1 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 18 / 209 (8.61%) | 79 / 211 (37.44%) | 3 / 28 (10.71%) |
| occurrences (all) | 27 | 145 | 3 |

| | | | |
|---|-------------------|-------------------|-----------------|
| Night sweats | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 5 / 211 (2.37%) | 1 / 28 (3.57%) |
| occurrences (all) | 13 | 7 | 1 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 11 / 209 (5.26%) | 39 / 211 (18.48%) | 2 / 28 (7.14%) |
| occurrences (all) | 17 | 44 | 2 |
| Pruritus | | | |
| subjects affected / exposed | 28 / 209 (13.40%) | 30 / 211 (14.22%) | 2 / 28 (7.14%) |
| occurrences (all) | 43 | 36 | 2 |
| Rash | | | |
| subjects affected / exposed | 62 / 209 (29.67%) | 45 / 211 (21.33%) | 3 / 28 (10.71%) |
| occurrences (all) | 114 | 61 | 3 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 13 / 209 (6.22%) | 8 / 211 (3.79%) | 3 / 28 (10.71%) |
| occurrences (all) | 20 | 13 | 3 |
| Skin lesion | | | |
| subjects affected / exposed | 13 / 209 (6.22%) | 10 / 211 (4.74%) | 0 / 28 (0.00%) |
| occurrences (all) | 17 | 15 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 3 / 209 (1.44%) | 2 / 211 (0.95%) | 2 / 28 (7.14%) |
| occurrences (all) | 3 | 2 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 57 / 209 (27.27%) | 68 / 211 (32.23%) | 6 / 28 (21.43%) |
| occurrences (all) | 100 | 102 | 15 |
| Back pain | | | |
| subjects affected / exposed | 30 / 209 (14.35%) | 34 / 211 (16.11%) | 3 / 28 (10.71%) |
| occurrences (all) | 41 | 35 | 4 |
| Muscle spasms | | | |
| subjects affected / exposed | 19 / 209 (9.09%) | 7 / 211 (3.32%) | 3 / 28 (10.71%) |
| occurrences (all) | 31 | 7 | 3 |
| Muscular weakness | | | |
| subjects affected / exposed | 5 / 209 (2.39%) | 4 / 211 (1.90%) | 2 / 28 (7.14%) |
| occurrences (all) | 5 | 4 | 2 |
| Musculoskeletal chest pain | | | |

| | | | |
|------------------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed | 14 / 209 (6.70%) | 11 / 211 (5.21%) | 0 / 28 (0.00%) |
| occurrences (all) | 15 | 12 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 19 / 211 (9.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 13 | 19 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 27 / 209 (12.92%) | 28 / 211 (13.27%) | 3 / 28 (10.71%) |
| occurrences (all) | 34 | 32 | 3 |
| Pain in extremity | | | |
| subjects affected / exposed | 34 / 209 (16.27%) | 38 / 211 (18.01%) | 3 / 28 (10.71%) |
| occurrences (all) | 45 | 55 | 4 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 8 / 211 (3.79%) | 1 / 28 (3.57%) |
| occurrences (all) | 15 | 9 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 11 / 209 (5.26%) | 2 / 211 (0.95%) | 0 / 28 (0.00%) |
| occurrences (all) | 30 | 3 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 12 / 209 (5.74%) | 11 / 211 (5.21%) | 2 / 28 (7.14%) |
| occurrences (all) | 21 | 14 | 4 |
| Influenza | | | |
| subjects affected / exposed | 17 / 209 (8.13%) | 7 / 211 (3.32%) | 5 / 28 (17.86%) |
| occurrences (all) | 27 | 11 | 6 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 28 / 209 (13.40%) | 21 / 211 (9.95%) | 4 / 28 (14.29%) |
| occurrences (all) | 53 | 34 | 6 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 16 / 209 (7.66%) | 7 / 211 (3.32%) | 1 / 28 (3.57%) |
| occurrences (all) | 25 | 7 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 29 / 209 (13.88%) | 7 / 211 (3.32%) | 2 / 28 (7.14%) |
| occurrences (all) | 50 | 9 | 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed | 30 / 209 (14.35%) | 28 / 211 (13.27%) | 5 / 28 (17.86%) |
| occurrences (all) | 38 | 30 | 7 |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 209 (2.39%) | 1 / 211 (0.47%) | 2 / 28 (7.14%) |
| occurrences (all) | 5 | 2 | 2 |

| Non-serious adverse events | All Patients | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 394 / 420 (93.81%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 18 / 420 (4.29%) | | |
| occurrences (all) | 23 | | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 34 / 420 (8.10%) | | |
| occurrences (all) | 44 | | |
| Skin papilloma | | | |
| subjects affected / exposed | 52 / 420 (12.38%) | | |
| occurrences (all) | 91 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 15 / 420 (3.57%) | | |
| occurrences (all) | 16 | | |
| Hypertension | | | |
| subjects affected / exposed | 85 / 420 (20.24%) | | |
| occurrences (all) | 122 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 60 / 420 (14.29%) | | |
| occurrences (all) | 92 | | |
| Chest pain | | | |
| subjects affected / exposed | 17 / 420 (4.05%) | | |
| occurrences (all) | 20 | | |
| Chills | | | |
| subjects affected / exposed | 98 / 420 (23.33%) | | |
| occurrences (all) | 284 | | |

| | | | |
|---|--------------------|--|--|
| Fatigue | | | |
| subjects affected / exposed | 161 / 420 (38.33%) | | |
| occurrences (all) | 213 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 31 / 420 (7.38%) | | |
| occurrences (all) | 96 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 66 / 420 (15.71%) | | |
| occurrences (all) | 93 | | |
| Pain | | | |
| subjects affected / exposed | 23 / 420 (5.48%) | | |
| occurrences (all) | 24 | | |
| Pyrexia | | | |
| subjects affected / exposed | 183 / 420 (43.57%) | | |
| occurrences (all) | 599 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 5 / 420 (1.19%) | | |
| occurrences (all) | 5 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 97 / 420 (23.10%) | | |
| occurrences (all) | 144 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 36 / 420 (8.57%) | | |
| occurrences (all) | 42 | | |
| Epistaxis | | | |
| subjects affected / exposed | 33 / 420 (7.86%) | | |
| occurrences (all) | 60 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 35 / 420 (8.33%) | | |
| occurrences (all) | 51 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 21 / 420 (5.00%) | | |
| occurrences (all) | 22 | | |

| | | | |
|--|------------------|--|--|
| Depression | | | |
| subjects affected / exposed | 22 / 420 (5.24%) | | |
| occurrences (all) | 22 | | |
| Insomnia | | | |
| subjects affected / exposed | 30 / 420 (7.14%) | | |
| occurrences (all) | 37 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 38 / 420 (9.05%) | | |
| occurrences (all) | 45 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 37 / 420 (8.81%) | | |
| occurrences (all) | 44 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 29 / 420 (6.90%) | | |
| occurrences (all) | 34 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 10 / 420 (2.38%) | | |
| occurrences (all) | 13 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 12 / 420 (2.86%) | | |
| occurrences (all) | 15 | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 12 / 420 (2.86%) | | |
| occurrences (all) | 15 | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 12 / 420 (2.86%) | | |
| occurrences (all) | 12 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 14 / 420 (3.33%) | | |
| occurrences (all) | 16 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 9 / 420 (2.14%) | | |
| occurrences (all) | 15 | | |

| | | | |
|--|--|--|--|
| Weight decreased subjects affected / exposed occurrences (all) | 32 / 420 (7.62%) 34 | | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Tendon rupture subjects affected / exposed occurrences (all) | 10 / 420 (2.38%) 14 3 / 420 (0.71%) 3 | | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all) | 6 / 420 (1.43%) 6 21 / 420 (5.00%) 24 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 47 / 420 (11.19%) 69 21 / 420 (5.00%) 23 138 / 420 (32.86%) 302 22 / 420 (5.24%) 24 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia | 38 / 420 (9.05%) 47 | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 10 / 420 (2.38%) | | |
| occurrences (all) | 11 | | |
| Neutropenia | | | |
| subjects affected / exposed | 28 / 420 (6.67%) | | |
| occurrences (all) | 37 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 13 / 420 (3.10%) | | |
| occurrences (all) | 13 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 9 / 420 (2.14%) | | |
| occurrences (all) | 10 | | |
| Eye disorders | | | |
| Blepharitis | | | |
| subjects affected / exposed | 4 / 420 (0.95%) | | |
| occurrences (all) | 4 | | |
| Cataract | | | |
| subjects affected / exposed | 8 / 420 (1.90%) | | |
| occurrences (all) | 12 | | |
| Dry eye | | | |
| subjects affected / exposed | 15 / 420 (3.57%) | | |
| occurrences (all) | 22 | | |
| Vision blurred | | | |
| subjects affected / exposed | 18 / 420 (4.29%) | | |
| occurrences (all) | 20 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 47 / 420 (11.19%) | | |
| occurrences (all) | 82 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 35 / 420 (8.33%) | | |
| occurrences (all) | 46 | | |
| Constipation | | | |
| subjects affected / exposed | 52 / 420 (12.38%) | | |
| occurrences (all) | 65 | | |
| Diarrhoea | | | |

| | | | |
|--|--------------------|--|--|
| subjects affected / exposed | 107 / 420 (25.48%) | | |
| occurrences (all) | 214 | | |
| Dry mouth | | | |
| subjects affected / exposed | 24 / 420 (5.71%) | | |
| occurrences (all) | 26 | | |
| Nausea | | | |
| subjects affected / exposed | 138 / 420 (32.86%) | | |
| occurrences (all) | 275 | | |
| Vomiting | | | |
| subjects affected / exposed | 89 / 420 (21.19%) | | |
| occurrences (all) | 185 | | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 27 / 420 (6.43%) | | |
| occurrences (all) | 59 | | |
| Alopecia | | | |
| subjects affected / exposed | 80 / 420 (19.05%) | | |
| occurrences (all) | 84 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 29 / 420 (6.90%) | | |
| occurrences (all) | 34 | | |
| Dry skin | | | |
| subjects affected / exposed | 65 / 420 (15.48%) | | |
| occurrences (all) | 76 | | |
| Eczema | | | |
| subjects affected / exposed | 29 / 420 (6.90%) | | |
| occurrences (all) | 33 | | |
| Erythema | | | |
| subjects affected / exposed | 41 / 420 (9.76%) | | |
| occurrences (all) | 49 | | |
| Hair texture abnormal | | | |
| subjects affected / exposed | 18 / 420 (4.29%) | | |
| occurrences (all) | 18 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 23 / 420 (5.48%) | | |
| occurrences (all) | 55 | | |

| | | | |
|---|--------------------|--|--|
| Hyperkeratosis | | | |
| subjects affected / exposed | 97 / 420 (23.10%) | | |
| occurrences (all) | 175 | | |
| Night sweats | | | |
| subjects affected / exposed | 17 / 420 (4.05%) | | |
| occurrences (all) | 21 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 50 / 420 (11.90%) | | |
| occurrences (all) | 63 | | |
| Pruritus | | | |
| subjects affected / exposed | 59 / 420 (14.05%) | | |
| occurrences (all) | 81 | | |
| Rash | | | |
| subjects affected / exposed | 109 / 420 (25.95%) | | |
| occurrences (all) | 178 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 24 / 420 (5.71%) | | |
| occurrences (all) | 36 | | |
| Skin lesion | | | |
| subjects affected / exposed | 23 / 420 (5.48%) | | |
| occurrences (all) | 32 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 7 / 420 (1.67%) | | |
| occurrences (all) | 7 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 127 / 420 (30.24%) | | |
| occurrences (all) | 217 | | |
| Back pain | | | |
| subjects affected / exposed | 67 / 420 (15.95%) | | |
| occurrences (all) | 80 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 29 / 420 (6.90%) | | |
| occurrences (all) | 41 | | |
| Muscular weakness | | | |

| | | | |
|-----------------------------------|-------------------|--|--|
| subjects affected / exposed | 11 / 420 (2.62%) | | |
| occurrences (all) | 11 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 25 / 420 (5.95%) | | |
| occurrences (all) | 27 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 31 / 420 (7.38%) | | |
| occurrences (all) | 33 | | |
| Myalgia | | | |
| subjects affected / exposed | 56 / 420 (13.33%) | | |
| occurrences (all) | 69 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 73 / 420 (17.38%) | | |
| occurrences (all) | 104 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 21 / 420 (5.00%) | | |
| occurrences (all) | 25 | | |
| Cystitis | | | |
| subjects affected / exposed | 13 / 420 (3.10%) | | |
| occurrences (all) | 33 | | |
| Folliculitis | | | |
| subjects affected / exposed | 25 / 420 (5.95%) | | |
| occurrences (all) | 39 | | |
| Influenza | | | |
| subjects affected / exposed | 28 / 420 (6.67%) | | |
| occurrences (all) | 44 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 50 / 420 (11.90%) | | |
| occurrences (all) | 93 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 24 / 420 (5.71%) | | |
| occurrences (all) | 33 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 38 / 420 (9.05%) | | |
| occurrences (all) | 61 | | |

| | | | |
|------------------------------------|-------------------|--|--|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 60 / 420 (14.29%) | | |
| occurrences (all) | 75 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 8 / 420 (1.90%) | | |
| occurrences (all) | 9 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 23 April 2012 | <p>Amendment No. 01:</p> <ol style="list-style-type: none">1. Included the statistical assumptions and analysis for the key secondary endpoint of OS.2. Included 'incidence of squamous cell carcinoma' in the endpoints.3. Included new requirements for subjects that remain on study treatment after radiographic disease progression4. Allowed patients to continue on trametinib/placebo after discontinuation of dabrafenib so that patients may have the opportunity to potentially continue an active therapy that is not otherwise available5. Required that study treatment will be interrupted for any treatment-related AE of Grade 36. Removed the use of topical steroids and topical/oral antibiotics from the prevention/prophylaxis of rash management for the first 28 days after study drug administration7. Required that rash of \geqgrade 3 must resolve to \leqgrade 1 before study treatment can be restarted8. Removed the allowance for palliative radiation and stated that subjects should not receive palliative radiotherapy prior to documented disease progression9. Added an ophthalmic exam at week 4 to enhance the monitoring and more accurately assess the incidence of ophthalmic toxicities10. Clarified that the LDH value collected within 14 days of randomization will be used for stratification11. Required that the overall response rate and the duration of response be calculated using only confirmed (not unconfirmed) responses12. Added bicarbonate and chloride to the clinical chemistry parameters13. Added additional assessments at screening and discontinuation to monitor for second primary malignancies other than cutaneous SCC14. Added assessments and a full skin examination to the brief physical exams15. Included minor changes for clarification and consistency throughout the protocol |
| 03 May 2012 | <p>Amendment No. 02:</p> <ul style="list-style-type: none">• Clarified: timings for ophthalmic exams and blood draws for cytokine analysis; requirements for cervical and rectal exams; acceptable toxicity levels for prior anti-cancer, treatment-related toxicities; requirements for whole-brain radiation; definition of asymptomatic hypertension, and definition of protocol specific SAE for new malignancies.• Added additional liver event follow up assessments to be consistent with GSK Oncology protocols.• Corrected typographical errors throughout and clerical errors in Appendix 8. |
| 26 June 2012 | <p>Amendment No. 03:</p> <ul style="list-style-type: none">• A country-specific amendment as requested by the French regulatory agency to modify the QTc withholding criteria and to add valvular toxicity withholding criteria for subjects enrolled in France. |

| | |
|-----------------|--|
| 08 January 2013 | <p>Amendment No. 04:</p> <ul style="list-style-type: none"> • Changed length of time contraception is required for males and females after permanently discontinuing study treatment based on emerging half-life data for trametinib. • Clarified that prothrombin time and partial thromboplastin time of >1.5 is acceptable at baseline for subjects receiving anticoagulant therapy. • Clarified that continuation of study treatment beyond radiographic (as defined by RECIST 1.1) or clinical disease progression may be possible. Note that this change does not affect the primary endpoint. • Clarified QTc stopping criteria. • Clarified collection frequency for blood samples for cytokine analysis. • Provided medical guidance for subjects with rigors/chills, but no fever. • Recommended that acetaminophen be used with caution in subjects with elevated liver enzymes. • Updated prohibited and cautionary medications. • Clarified that the informed consent may be signed >28 days prior to randomization. • Clarified that the Quality of Life assessment after disease progression also applies to subjects that have progressed but remain on study treatment. • Clarified assessments schedule for subjects that have withdrawn from study treatment prior to progression. • Removed language indicating that nodal lesions are measurable by X-ray. • Defined the intensity of hypotension required for a pyrexia-related SAE. • Performed clerical and administrative changes. |
| 22 April 2013 | <p>Amendment No. 05:</p> <ul style="list-style-type: none"> • Administrative changes including updated Sponsor Contact information. • Per FDA request, clarified criteria for allowing patients to continue study treatment after disease progression. • Updated concomitant medications based on emerging data. |
| 20 May 2013 | <p>Amendment No. 06:</p> <ul style="list-style-type: none"> • Updated the Data Analysis and Statistical Considerations (Section 9) to address the impact of over enrollment. |
| 14 October 2013 | <p>Amendment No. 07:</p> <ul style="list-style-type: none"> • As requested by the European Regulatory Authority, information for new malignancies will be collected throughout study treatment and follow-up. • As requested by French Regulatory Authority, additional monitoring following discontinuation of dabrafenib was incorporated • Administrative changes |
| 12 August 2014 | <p>Amendment No. 08:</p> <ul style="list-style-type: none"> • Administrative changes including updating medical monitors and formatting. • To obtain long-term survival data, increased the time to study closure. • To ensure optimum dosing, provided drug-specific instructions in cases where a dose is missed. • Based on emerging data, updated list of concomitant medications and stipulated that oral contraceptives are not permitted for use as contraceptives. • To improve management of adverse events, the following dose modification guidelines were modified and/or clarified based on emerging data: LVEF, HTN, QTc prolongation, hand-foot skin reactions, cuSCC, pyrexia, renal insufficiency, visual changes, and pneumonitis. Guidelines for new primary melanoma, non-cutaneous malignancies, pancreatitis, hyperglycemia, and retinal pigment epithelial detachment (RPED), which replaces the AE of CSR, were added. • Removed blood sample collection during pyrexia event for cytokine analysis as sufficient sampling has been achieved. • Clarified treatment of study-treatment overdose regarding hemodialysis. • Due to the amount of censoring at the primary analysis, a descriptive analysis of PFS, DoR, and ORR will be conducted at the final analysis. • Based on feedback from the FDA, the final OS analysis will be performed at 220 events rather than 275. A descriptive OS update will be performed when 275 events have occurred. • To facilitate access to the combination therapy, text was added that will allow eligible subjects to crossover to the combination therapy if a statistically significant and clinically meaningful OS benefit is observed at the final OS analysis. |

| | |
|------------------|--|
| 07 November 2016 | Amendment No. 09: <ul style="list-style-type: none"> • Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. • Make administrative changes to align with Novartis processes and procedures. |
| 27 November 2017 | Amendment No. 10: <ul style="list-style-type: none"> • Reduce frequency of RECIST v1.1 assessments after Week 56; from "every 12 weeks" to "as clinically indicated (at least every 24 weeks)". • Clarify that the lesion assessment scan collection has been stopped for all scans performed after 12 January 2015 (interim analysis cutoff date) since 22 April 2015 • Add a contraception requirement for male participants. • Administrative changes: change Novartis staff names and contact details. Replace a reference to GSK, missed in previous amendment, with that of Novartis |

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.

New malignancies and AEs possibly related to study treatment were collected even if they occurred more than 30 days post-treatment.

Notes: