



Clinical trial results:

A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-001161-41 |
| Trial protocol | GB NO DE ES NL IT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 21 October 2016 |
| First version publication date | 21 October 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 113928 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

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 | Interim |
| Date of interim/final analysis | 27 April 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 October 2015 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the overall response rate (ORR) in subjects with stage IV BRAF V600E mutant non-small cell lung cancer administered dabrafenib as a single agent (Cohort A) and in combination with trametinib (Cohorts B and C)

Protection of trial subjects:

Participants in this study received supportive care according to standard medical practice.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 20 June 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Japan: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 15 |
| Country: Number of subjects enrolled | Taiwan: 3 |
| Country: Number of subjects enrolled | France: 57 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Netherlands: 22 |
| Country: Number of subjects enrolled | Norway: 1 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | United States: 41 |
| Worldwide total number of subjects | 166 |
| EEA total number of subjects | 104 |

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) | 71 |
| From 65 to 84 years | 88 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details:

Eligible participants (par.) were enrolled in Cohort (Coh) A (monotherapy [Dabrafenib{DAB}]). Par. in Coh-A who had disease progression and adequately tolerating DAB were given option to crossover to Coh-B who received combination therapy (DAB+Trametinib). In Coh-C, par. without prior anti-cancer treatment received combination therapy.

Pre-assignment

Screening details:

Par. with metastatic non-small cell lung cancer (NSCLC) were screened and allocated to Coh-A (DAB twice daily [BID] i.e. monotherapy), Coh-B (Combination Second-Line Plus) and Coh-C (Combination First-Line) according to their eligibility. The results presented are based on the Interim Analysis.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Monotherapy All Treated |

Arm description:

Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Product 1 |
| Investigational medicinal product code | Dabrafenib (GSK2118436) |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

It will be provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) capsules. Dabrafenib will be administered as a single agent in all cohorts.

| | |
|------------------|------------------------------|
| Arm title | Combination Second-Line Plus |
|------------------|------------------------------|

Arm description:

Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Product 1 |
| Investigational medicinal product code | Trametinib (GSK1120212) |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

It will be provided as 0.5 mg and 2 mg tablets. Trametinib will be administered in combination with dabrafenib in Cohorts B and C

| | |
|------------------|------------------------|
| Arm title | Combination First-Line |
|------------------|------------------------|

Arm description:

Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable

AEs or at investigator discretion to discontinue.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Product 1 |
| Investigational medicinal product code | Trametinib (GSK1120212) |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

It will be provided as 0.5 mg and 2 mg tablets. Trametinib will be administered in combination with dabrafenib in Cohorts B and C

| | |
|--|-------------------------|
| Investigational medicinal product name | Product 1 |
| Investigational medicinal product code | Dabrafenib (GSK2118436) |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

It will be provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) capsules. Dabrafenib will be administered as a single agent in all cohorts.

| Number of subjects in period 1 | Monotherapy All Treated | Combination Second-Line Plus | Combination First-Line |
|---------------------------------------|--------------------------------|-------------------------------------|-------------------------------|
| Started | 84 | 57 | 25 |
| Completed | 0 | 0 | 0 |
| Not completed | 84 | 57 | 25 |
| Adverse event, serious fatal | 57 | 23 | 1 |
| Consent withdrawn by subject | 6 | - | - |
| Transferred to Other Arm/Group | 8 | - | - |
| Ongoing | 10 | 32 | 24 |
| Lost to follow-up | 3 | 2 | - |

Baseline characteristics

Reporting groups

| | |
|--|------------------------------|
| Reporting group title | Monotherapy All Treated |
| Reporting group description: | |
| Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy. | |
| Reporting group title | Combination Second-Line Plus |
| Reporting group description: | |
| Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue. | |
| Reporting group title | Combination First-Line |
| Reporting group description: | |
| Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable AEs or at investigator discretion to discontinue. | |

| Reporting group values | Monotherapy All Treated | Combination Second-Line Plus | Combination First-Line |
|---|-------------------------|------------------------------|------------------------|
| Number of subjects | 84 | 57 | 25 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| arithmetic mean | 64.8 | 65.1 | 70.8 |
| standard deviation | ± 10.51 | ± 10.14 | ± 9.5 |
| Gender categorical | | | |
| Gender categorical description | | | |
| Units: Subjects | | | |
| Female | 44 | 28 | 15 |
| Male | 40 | 29 | 10 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian - East Asian Heritage | 14 | 3 | 1 |
| Asian - Central/South Asian Heritage | 2 | 0 | 0 |
| Asian - Japanese Heritage | 2 | 1 | 0 |
| African American/African Heritage | 2 | 2 | 0 |
| Native Hawaiian Or Other Pacific Islander | 0 | 0 | 1 |
| White - Arabic/North African Heritage | 2 | 2 | 0 |
| White - White/Caucasian/European Heritage | 62 | 47 | 23 |
| Other-African American/African Heritage | 0 | 1 | 0 |
| Other-missing | 0 | 1 | 0 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 166 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Gender categorical description | | | |
| Units: Subjects | | | |
| Female | 87 | | |
| Male | 79 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian - East Asian Heritage | 18 | | |
| Asian - Central/South Asian Heritage | 2 | | |
| Asian - Japanese Heritage | 3 | | |
| African American/African Heritage | 4 | | |
| Native Hawaiian Or Other Pacific Islander | 1 | | |
| White - Arabic/North African Heritage | 4 | | |
| White - White/Caucasian/European Heritage | 132 | | |
| Other-African American/African Heritage | 1 | | |
| Other-missing | 1 | | |

End points

End points reporting groups

| | |
|---|------------------------------|
| Reporting group title | Monotherapy All Treated |
| Reporting group description: Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy. | |
| Reporting group title | Combination Second-Line Plus |
| Reporting group description: Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue. | |
| Reporting group title | Combination First-Line |
| Reporting group description: Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable AEs or at investigator discretion to discontinue. | |
| Subject analysis set title | Monotherapy Second-Line Plus |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy. | |
| Subject analysis set title | Combination Second-Line Plus |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue. | |
| Subject analysis set title | Combination First-Line |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable AEs or at investigator discretion to discontinue. | |

Primary: Percentage of participants with overall response rate (ORR) at the date of analysis

| | |
|---|---|
| End point title | Percentage of participants with overall response rate (ORR) at the date of analysis ^{[1][2]} |
| End point description: ORR is defined as the percentage of par. with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1. RECIST criteria evaluates the response on the basis of target and non-target lesions, and best over all response. The response rate was analyzed every 6 weeks (wks) after initiation of study treatment until Week 36 and then every 12 wks. Percentage of par. analyzed as number of par. having overall response on the date of analysis from Baseline multiply by 100. The Second Line Plus All Treated Population used for cohort A and B consisted of all par. in the All Treated Population who had received at least one line of prior anti-cancer therapy for advanced/metastatic disease. The First-Line All Treated Population used for cohort C consisted of all par. in the All Treated Population who had not received any prior anti-cancer therapy for advanced/metastatic disease. | |
| End point type | Primary |
| End point timeframe: Arm 1: From First dose until 21-Nov-2014; Arm 2 and 3: From first dose until 07-Oct-2015. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis is available.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis is available.

| End point values | Combination Second-Line Plus | Monotherapy Second-Line Plus | Combination First-Line | |
|-----------------------------------|------------------------------------|------------------------------------|---------------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 57 ^[3] | 78 | 15 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 63.2 (49.3 to 75.6) | 33.3 (23.1 to 44.9) | 53.3 (26.6 to 78.7) | |

Notes:

[3] - Second-Line All Treated Population for Coh-A and Coh-B / First-Line All Treated Population for Coh-C

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) at the date of analysis

| | |
|-----------------|---|
| End point title | Duration of response (DoR) at the date of analysis ^[4] |
|-----------------|---|

End point description:

DoR is defined for the subset of participants with confirmed CR or PR, as the time from first documented evidence of CR or PR until time of first documented disease progression or death due to any cause. The response was analyzed every 6 weeks after initiation of study treatment until Week 36 and then every 12 wks. Disease progression will be based on radiological assessments magnetic resonance imaging (MRI) or computed tomography (CT). Confidence Intervals estimated using the Brookmeyer Crowley method. Upper limit of confidence interval was not reached as data were not yet mature. The data for Cohort C is not posted as study is ongoing. Second-Line All Treated Population for Coh-A and Coh-B, and First-Line All Treated Population for Coh-C.

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

End point timeframe:

Arm 1: From First dose until 21-Nov-2014; Arm 2 and 3: From first dose until 07-Oct-2015

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis is available.

| End point values | Combination Second-Line Plus | Monotherapy Second-Line Plus | Combination First-Line | |
|----------------------------------|------------------------------------|------------------------------------|---------------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 36 | 26 | 0 ^[5] | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9 (6.9 to 18.3) | 9.6 (5.4 to 15.2) | (to) | |

Notes:

[5] - The data for Cohort C is not posted as study is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) at the date of analysis

| | |
|-----------------|---|
| End point title | Progression free survival (PFS) at the date of analysis |
|-----------------|---|

End point description:

PFS is defined as the interval between first dose and the earliest date of disease progression or death due to any cause. The target and non-target lesions were identified at time of screening and the same lesions were re-assessed by a contrast-enhanced brain magnetic resonance imaging or Computed tomography every 6 wks after initiation of study treatment until Week 36 and then every 12 wks. Confidence Intervals estimated using the Brookmeyer Crowley method. The data for Cohort C is not posted as study is ongoing. First-Line Second-Line All Treated Population for Coh-A and Coh-B, and First-Line All Treated Population for Coh-C.

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

End point timeframe:

Arm 1: From First dose until 21-Nov-2014; Arm 2 and 3: From first dose until 07-Oct-2015

| End point values | Monotherapy Second-Line Plus | Combination Second-Line Plus | Combination First-Line | |
|----------------------------------|------------------------------------|------------------------------------|---------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 78 | 57 | 0 ^[6] | |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.5 (3.4 to 7.3) | 9.7 (6.9 to 19.6) | (to) | |

Notes:

[6] - The data for Cohort C is not posted as study is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at the date of analysis

| | |
|-----------------|--|
| End point title | Overall survival (OS) at the date of analysis ^[7] |
|-----------------|--|

End point description:

OS defined as the time from first dose until death due to any cause. Confidence Intervals estimated using the Brookmeyer Crowley method. The data for Cohort C is not posted as study is ongoing. A value of "99999" indicates where no data is available or not able to determine the value. First-LineSecond-Line All Treated Population for Coh-A and Coh-B, and First-Line All Treated Population for Coh-C.

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

End point timeframe:

Arm 1 and 2: From First dose until 07-Oct-2015

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis is available.

| End point values | Combination Second-Line Plus | Monotherapy Second-Line Plus | Combination First-Line | |
|----------------------------------|------------------------------------|------------------------------------|---------------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 57 | 78 | 0 ^[8] | |
| Units: Months | | | | |
| median (confidence interval 95%) | 17.6 (14.3 to 99999) | 12.7 (7.3 to 16.3) | (to) | |

Notes:

[8] - The data for Cohort C is not posted as study is ongoing.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events will be collected from time the first study dose is administered until 30 days following discontinuation of study treatment.

Adverse event reporting additional description:

Adverse events will be graded according to the common terminology criteria for adverse events (CTCAE), version 4. For participants in the Crossover Population, any treatment-emergent AEs related to the initiation of combination treatment will be summarized for Crossover Population only.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Monotherapy |
|-----------------------|-------------|

Reporting group description:

Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

| | |
|-----------------------|---------------------|
| Reporting group title | Combination Therapy |
|-----------------------|---------------------|

Reporting group description:

Combination of participants who had received 1-3 prior lines of systemic anti-cancer therapies and participants who had not received any prior systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.

| Serious adverse events | Monotherapy | Combination Therapy | |
|---|------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 84 (42.86%) | 38 / 82 (46.34%) | |
| number of deaths (all causes) | 1 | 4 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 4 / 84 (4.76%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Keratoacanthoma | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 8 / 84 (9.52%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 8 / 8 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------|----------------|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |

| | | | |
|---|----------------|------------------|--|
| subjects affected / exposed | 5 / 84 (5.95%) | 10 / 82 (12.20%) | |
| occurrences causally related to treatment / all | 3 / 6 | 9 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Anxiety | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paresis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 3 / 82 (3.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic thrombosis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal dystrophy | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uveitis | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haemorrhage | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery thrombosis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Renal failure | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Furuncle | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Influenza | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Legionella infection | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 2 / 82 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 82 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 82 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Monotherapy | Combination Therapy | |
|---|------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 82 / 84 (97.62%) | 77 / 82 (93.90%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Keratoacanthoma | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 0 / 82 (0.00%) | |
| occurrences (all) | 6 | 0 | |

| | | | |
|--|------------------|------------------|--|
| Acrochordon | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 0 / 82 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 9 / 84 (10.71%) | 2 / 82 (2.44%) | |
| occurrences (all) | 12 | 3 | |
| Papilloma | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 0 / 82 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 8 / 84 (9.52%) | 2 / 82 (2.44%) | |
| occurrences (all) | 10 | 2 | |
| Skin papilloma | | | |
| subjects affected / exposed | 23 / 84 (27.38%) | 1 / 82 (1.22%) | |
| occurrences (all) | 40 | 1 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 3 / 82 (3.66%) | |
| occurrences (all) | 6 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 7 / 82 (8.54%) | |
| occurrences (all) | 6 | 8 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 25 / 84 (29.76%) | 18 / 82 (21.95%) | |
| occurrences (all) | 31 | 20 | |
| Chest pain | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 5 / 82 (6.10%) | |
| occurrences (all) | 7 | 6 | |
| Chills | | | |
| subjects affected / exposed | 12 / 84 (14.29%) | 15 / 82 (18.29%) | |
| occurrences (all) | 15 | 20 | |
| Fatigue | | | |
| subjects affected / exposed | 25 / 84 (29.76%) | 14 / 82 (17.07%) | |
| occurrences (all) | 27 | 16 | |
| Malaise | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 5 / 84 (5.95%) | 5 / 82 (6.10%) | |
| occurrences (all) | 5 | 6 | |
| Oedema | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 5 / 82 (6.10%) | |
| occurrences (all) | 2 | 6 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 3 / 82 (3.66%) | |
| occurrences (all) | 6 | 4 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 19 / 82 (23.17%) | |
| occurrences (all) | 7 | 24 | |
| Pain | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 5 / 82 (6.10%) | |
| occurrences (all) | 2 | 5 | |
| Pyrexia | | | |
| subjects affected / exposed | 29 / 84 (34.52%) | 33 / 82 (40.24%) | |
| occurrences (all) | 43 | 81 | |
| Xerosis | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | 4 / 82 (4.88%) | |
| occurrences (all) | 7 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 24 / 84 (28.57%) | 14 / 82 (17.07%) | |
| occurrences (all) | 30 | 15 | |
| Dysphonia | | | |
| subjects affected / exposed | 8 / 84 (9.52%) | 1 / 82 (1.22%) | |
| occurrences (all) | 8 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 17 / 84 (20.24%) | 11 / 82 (13.41%) | |
| occurrences (all) | 19 | 12 | |
| Haemoptysis | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | 4 / 82 (4.88%) | |
| occurrences (all) | 7 | 4 | |
| Productive cough | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 6 | 6 / 82 (7.32%) 8 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 6 | 6 / 82 (7.32%) 6 | |
| Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 15 / 84 (17.86%) 15 0 / 84 (0.00%) 0 | 8 / 82 (9.76%) 9 9 / 82 (10.98%) 10 7 / 82 (8.54%) 7 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 7 / 84 (8.33%) 7 4 / 84 (4.76%) 4 16 / 84 (19.05%) 18 | 8 / 82 (9.76%) 9 6 / 82 (7.32%) 8 10 / 82 (12.20%) 15 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia | 10 / 84 (11.90%) 11 6 / 84 (7.14%) 7 2 / 84 (2.38%) 2 | 8 / 82 (9.76%) 9 2 / 82 (2.44%) 2 11 / 82 (13.41%) 24 | |

| | | | |
|---|---|---|--|
| subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 | 4 / 82 (4.88%) 5 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 5 / 82 (6.10%) 9 | |
| Eye disorders Vision blurred subjects affected / exposed occurrences (all) Visual acuity reduced subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 3 / 84 (3.57%) 3 | 1 / 82 (1.22%) 3 5 / 82 (6.10%) 6 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting | 8 / 84 (9.52%) 10 2 / 84 (2.38%) 2 9 / 84 (10.71%) 9 16 / 84 (19.05%) 22 1 / 84 (1.19%) 1 2 / 84 (2.38%) 2 24 / 84 (28.57%) 31 | 3 / 82 (3.66%) 3 7 / 82 (8.54%) 10 13 / 82 (15.85%) 15 22 / 82 (26.83%) 37 5 / 82 (6.10%) 5 6 / 82 (7.32%) 6 32 / 82 (39.02%) 49 | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 18 / 84 (21.43%) | 23 / 82 (28.05%) | |
| occurrences (all) | 26 | 54 | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 10 / 84 (11.90%) | 4 / 82 (4.88%) | |
| occurrences (all) | 17 | 4 | |
| Alopecia | | | |
| subjects affected / exposed | 18 / 84 (21.43%) | 5 / 82 (6.10%) | |
| occurrences (all) | 18 | 5 | |
| Dry skin | | | |
| subjects affected / exposed | 21 / 84 (25.00%) | 19 / 82 (23.17%) | |
| occurrences (all) | 23 | 22 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 5 / 82 (6.10%) | |
| occurrences (all) | 1 | 6 | |
| Hair texture abnormal | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | 3 / 82 (3.66%) | |
| occurrences (all) | 7 | 3 | |
| Madarosis | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 0 / 82 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 25 / 84 (29.76%) | 6 / 82 (7.32%) | |
| occurrences (all) | 55 | 6 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 19 / 84 (22.62%) | 3 / 82 (3.66%) | |
| occurrences (all) | 22 | 4 | |
| Papule | | | |
| subjects affected / exposed | 8 / 84 (9.52%) | 2 / 82 (2.44%) | |
| occurrences (all) | 8 | 2 | |
| Pruritus | | | |
| subjects affected / exposed | 12 / 84 (14.29%) | 10 / 82 (12.20%) | |
| occurrences (all) | 12 | 16 | |
| Rash | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 16 / 84 (19.05%) | 15 / 82 (18.29%) | |
| occurrences (all) | 16 | 21 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 0 / 82 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Rash papular | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 3 / 82 (3.66%) | |
| occurrences (all) | 6 | 3 | |
| Skin lesion | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 2 / 82 (2.44%) | |
| occurrences (all) | 8 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 16 / 84 (19.05%) | 12 / 82 (14.63%) | |
| occurrences (all) | 25 | 14 | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 6 / 82 (7.32%) | |
| occurrences (all) | 2 | 7 | |
| Back pain | | | |
| subjects affected / exposed | 10 / 84 (11.90%) | 7 / 82 (8.54%) | |
| occurrences (all) | 11 | 9 | |
| Muscular weakness | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 1 / 82 (1.22%) | |
| occurrences (all) | 7 | 1 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 2 / 82 (2.44%) | |
| occurrences (all) | 7 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 12 / 84 (14.29%) | 9 / 82 (10.98%) | |
| occurrences (all) | 15 | 12 | |
| Pain in extremity | | | |
| subjects affected / exposed | 15 / 84 (17.86%) | 3 / 82 (3.66%) | |
| occurrences (all) | 17 | 3 | |
| Infections and infestations | | | |

| | | | |
|---|------------------------|------------------------|--|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 9 / 84 (10.71%) 10 | 5 / 82 (6.10%) 7 | |
| Bronchitis subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 7 | 5 / 82 (6.10%) 8 | |
| Rhinitis subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 6 | 5 / 82 (6.10%) 6 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 7 / 84 (8.33%) 7 | 1 / 82 (1.22%) 1 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 6 | 6 / 82 (7.32%) 6 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 23 / 84 (27.38%) 30 | 19 / 82 (23.17%) 21 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 6 | 3 / 82 (3.66%) 4 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 8 | 5 / 82 (6.10%) 5 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 3 / 84 (3.57%) 4 | 7 / 82 (8.54%) 9 | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 11 | 5 / 82 (6.10%) 5 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 31 May 2011 | Updated the inclusion / exclusion criteria, updated the QTc withdrawal criteria and the Dose Modification section, added an Independent Data Monitoring Committee. In addition, language specific to French sites was added. Throughout the protocol, minor administrative and typographical changes were made. |
| 13 October 2011 | Increased the frequency of cardiac monitoring from every 12 weeks to every 9 weeks. Other clarifications to the PGx sections in the main text and in Appendix 1, description of physical exam and list of laboratory tests were made. Guidelines for management of renal insufficiency were added. A baseline sample for cytokine profiling was added (in the event a subject develops fever, the baseline cytokine values are available). |
| 30 April 2012 | Is a country specific amendment that changed the QTc stopping criteria to 500 msec for UK subjects and clarified the definition of abstinence |
| 15 June 2012 | Changed Inclusion to clarify that the failed chemotherapy regimen must have been a platinum-based chemotherapy; changed Exclusion Criteria #9 regarding the length of time a subject must be disease free from 5 years to 3 years; allowed for continued treatment with GSK2118436 beyond disease progression; updated the Dose Modification Guidelines for Fever and the Renal Insufficiency Guidelines for consistency with the current asset-specific language; added the UK to Appendix 3 (country-specific QTc stopping criteria of 500 msec); clarified restrictions on certain foods known to affect drug metabolism; clarified when an MRI or CT is required at baseline and on-study; removed the requirement for males who choose abstinence as their contraceptive method to begin abstinence 14 days BEFORE administration of GSK2118436; clarified the definition of abstinence; fixed T&E footnotes, lessened the frequency of efficacy assessments beginning at Week 36 and onwards, and removed the ANC measurement on Day 8; clarified SAE language for consistency with current asset language. |
| 20 August 2012 | Updated the Background section (Section 1.1) to include the currently available safety and efficacy data for GSK2118436; changed Inclusion Criterion (#7) to clarify for the reader that additional details on mutation testing and central confirmation of mutation testing are provided in Section 7.1.1; changes to Section 7.1.1 included clarification on BRAF mutation testing and intent that all subject have tissue available for central confirmation (when testing at inclusion is performed at a local laboratory) (also affected T&E footnote); removed the requirement for men to use contraception (Inclusion Criterion #9 and Section 7.4.2); changed the limit for use of anti-cancer treatment prior to dosing with GSK2118436 from 28 days to 14 days (Exclusion Criteria #2 and #3); added defined safety and efficacy criteria that need to be met in order to allow treatment with GSK2118436 beyond disease progression (Section 4.2.1); updated Section 5.7, Guidelines for Dose Modification and Events of Special Interest, in line with current asset language; clarified QTc Stopping Criteria to delineate QTcF v QTcB and QTc uncorrected stopping values; and clarified protocol-specific SAE language for consistency with current asset language (removed LVEF stopping criteria as a protocol specific SAE). |
| 24 January 2013 | Is a country specific amendment for France and the UK that specifies QTc stopping criteria in Appendix 3. Footnotes to the Time and Events Table were also renumbered. |

| | |
|-------------------|--|
| 16 April 2013 | Added the study expansion cohort (n=20) increasing total sample size to 60 subjects, updated the eligibility criteria to remove the requirement of disease progression on a platinum-based chemotherapy prior to study enrollment to allow inclusion of first line metastatic patients in the expansion cohort and allow subjects with HCV clearance, updated QTc stopping criteria, removed herbal remedies as a prohibitive medication (St Johns Wort still prohibited), updated the prohibitive and cautionary medication list, increased the frequency of dermatologic assessments to every 9 weeks, changed blood sample for cfDNA at disease progression from optional to required, replaced "GSK2118436" with "dabrafenib" throughout the document and additional administrative level clarifications and edits. Section 1.2.1 deleted, please refer to the Dabrafenib Investigator's Brochure for all background/clinical trial information on dabrafenib. |
| 25 September 2013 | Added the dabrafenib/trametinib combination therapy cohort (n=40) increasing the total sample size to 100 subjects, ophthalmic examination added at screening, Week 6 and as clinically necessary thereafter for combination treatment only, combination cohort specific inclusion/exclusion criteria added, combination cohort specific dose modification and toxicity management guidelines added, option to crossover from monotherapy to combination treatment at time of radiologic disease progression added, ECHO and ECG schedule clarified as baseline, Week 6 and every 9 weeks thereafter |
| 14 October 2014 | Updated secondary medical monitor. Added Cohort C to enroll 25 first line subjects. Additional language added to study rationale in Section 1.2.1. Revised required laboratory value for PT/INR and PTT in Section 4.1.2. Removed HIV from Exclusion Criterion #7 and revised Exclusion Criterion #15 in Section 4.1.3. Additional language added to Section 4.2.1 and Section 4.2.3 to clarify requirements for continuing study treatment post-PD and for crossover requirements. Updated dose modification and toxicity management language throughout Section 5.9. Updated general dose modification guidelines in Section 5.9.2. Updated dose modification guidelines and stopping criteria for LVEF in Section 5.10.1. Updated liver chemistry stopping and follow-up criteria in Section 5.10.3. Guidelines for holding study drug following radiation treatment added to Section 6.1. Specified that body fluid sample (e.g., pleural effusion) is not acceptable for BRAF mutation testing sample in Section 7.1.1. Added confirmation of measurable disease by independent review at baseline prior to enrolment in Section 7.1.2. Updated language regarding ophthalmic examination requirements in Section 7.3.2.3. Added language in Section 7.3.2.9.2 allowing investigator to decide if basal cell carcinoma should be reported as SAE or not. Specified in Section 7.4.1 that females should wait at least 4 months after last dose of the combination therapy before nursing. Specified in Section 7.7 that body fluid sample (e.g., pleural effusion) is not preferred for PD biomarker sample. Added Section 9.1.3 to describe hypothesis and study design for Cohort C. Updated Section 9.2 regarding Cohort C. Updated Investigator Brochures citations to current versions. Appendix 4 added regarding additional monitoring requirements for subjects in France only. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported